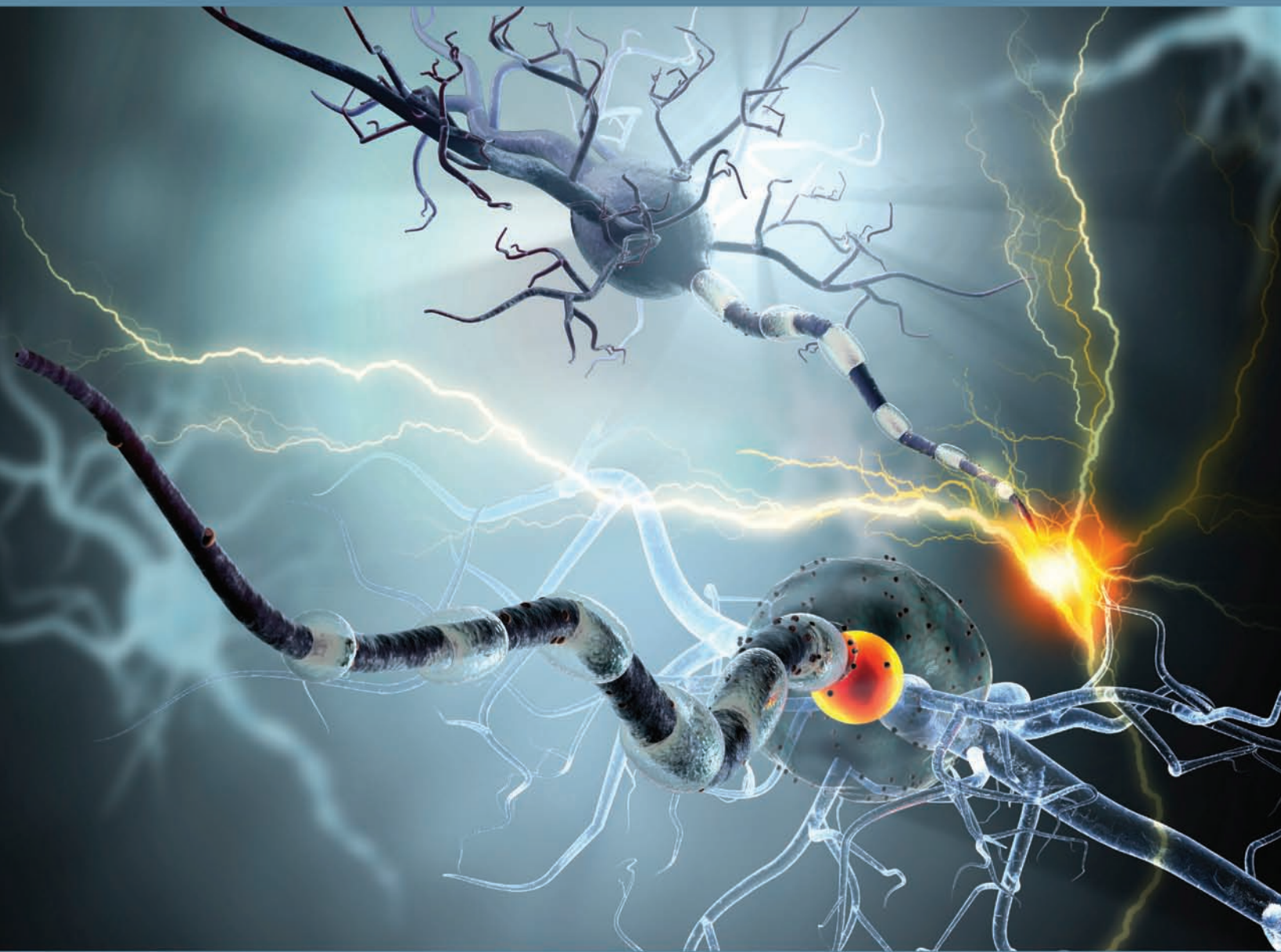


# PRACTICAL EPILEPSY



**Aatif M. Husain**



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# Practical Epilepsy



# Practical Epilepsy

## EDITOR

AATIF M. HUSAIN, MD  
Department of Neurology  
Duke University Medical Center  
Durham, North Carolina  
Neurodiagnostic Center  
Veterans Administration Medical Center  
Durham, North Carolina



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*This book is dedicated to my wife, Sarwat Mohsin Husain, who gives so much  
and asks for so little. Without her, there would be... nothing.*



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# Contributors

**William L. Bell, MD**

Professor and Director of Comprehensive  
Epilepsy Center  
Department of Neurology  
Georgetown University  
Washington, DC

**Robbie D. Buechler, MD, PhD**

Neurologist  
Department of Neurosciences/Neurology  
Novant Health Neurology Specialists  
Matthews, North Carolina

**José E. Cavazos, MD, PhD**

Professor and Assistant Dean  
Department of Neurology  
University of Texas Health Science Center at  
San Antonio;  
Staff Physician and Director  
San Antonio VA Epilepsy Center of Excellence  
South Texas Veterans Health Care System  
San Antonio, Texas

**Merlise Clyde, PhD**

Professor  
Department of Statistical Science  
Duke University  
Durham, North Carolina

**Timothy A. Collins, MD**

Associate Professor of Neurology  
Chief, Division of Headache and Pain  
Department of Neurology  
Duke University Medical Center  
Durham, North Carolina

**Sarah E. Cook, PhD**

Assistant Professor  
Department of Psychiatry and Behavioral Sciences  
Duke University  
Durham, North Carolina

**Keith E. Dombrowski, MD**

Assistant Professor  
Department of Neurology  
Duke University Medical Center;  
Neurologist  
Department of Medicine  
Durham VA Medical Center  
Durham, North Carolina

**William B. Gallentine, DO**

Associate Professor  
Division of Pediatric Neurology  
Department of Pediatrics  
Duke Children's Hospital  
Durham, North Carolina

**David B. Goldstein, PhD**

Professor  
Department of Genetics and Development;  
Director  
Institute for Genomic Medicine  
Columbia University Medical Center  
New York, New York

**Gerald Grant, MD**

Associate Professor  
Department of Neurosurgery  
Stanford University  
Stanford, California

**Michael Haglund, MD, PhD**

Professor  
Division of Neurosurgery  
Department of Surgery  
Duke University Medical Center  
Durham, North Carolina

**Jonathan J. Halford, MD**

Associate Professor of Neurology and Psychiatry  
Department of Neurology  
Medical University of South Carolina  
Charleston, South Carolina

**Abeer J. Hani, MD**

Assistant Professor  
Division of Pediatric Neurology  
Department of Pediatrics  
Gilbert and Rose-Marie Chagoury School of Medicine  
Lebanese American University  
Beirut, Lebanon

**Erin L. Heinzen, PharmD, PhD**

Assistant Professor  
Department of Pathology;  
Deputy Director  
Institute for Genomic Medicine  
Columbia University Medical Center  
New York, New York

**Susan Hollar, BA, REEGT**

Epilepsy Program Manager  
Department of Neurology  
University of Kentucky  
Lexington, Kentucky

**Aatif M. Husain, MD**

Professor  
Department of Neurology  
Duke University Medical Center;  
Director  
Neurodiagnostic Center  
Veterans Administration Medical Center  
Durham, North Carolina

**Kathryn Idol Xixis, MD**

Fellow  
Division of Pediatric Neurology  
Department of Pediatrics  
Duke University Medical Center  
Durham, North Carolina

**Sujay M. Kansagra, MD**

Assistant Professor  
Division of Pediatric Neurology  
Department of Pediatrics  
Duke University Medical Center  
Durham, North Carolina

**Roha Khalid, MD**

Fellow  
Division of Pediatric Neurology  
Department of Pediatrics  
Duke University Medical Center  
Durham, North Carolina

**Sanjeev V. Kothare, MD**

Director, Pediatric Sleep Program  
Senior Epileptologist and Pediatric Neurologist  
Professor of Neurology  
New York University Medical Center and Langone School  
of Medicine  
New York, New York

**Deborah LaBelle-Scarfo, RN, BSN, CNRN**

Nurse Clinician  
Duke Neurodiagnostic Services/Epilepsy Center  
Duke University Hospital  
Durham, North Carolina

**David M. Labiner, MD**

Professor and Head  
Department of Neurology  
The University of Arizona  
Tucson, Arizona

**Lynn Liu, MD**

Associate Professor  
Departments of Neurology, Pediatrics and Anesthesiology  
Strong Epilepsy Center  
University of Rochester Medical Center  
Rochester, New York

**Matthew W. Luedke, MD**

Instructor  
Department of Neurology  
Duke University Hospital  
Durham, North Carolina

**Mohamad A. Mikati, MD**

Wilburt C. Davison Distinguished Professor of Pediatrics  
Professor of Neurobiology  
Chief, Division of Pediatric Neurology  
Department of Pediatrics/Pediatric Neurology  
Duke University Medical Center  
Durham, North Carolina

**K. Nicole Mims, MD**

Physician  
Department of Sleep  
Charlotte Medical Clinic at Carolinas Healthcare Systems  
Charlotte, North Carolina

**Richard P. Morse, MD**

Chief of Child Neurology and Development  
Department of Pediatrics  
Children's Hospital at Dartmouth  
Dartmouth-Hitchcock Medical Center  
Lebanon, New Hampshire

**Jorge Oldan, MD**

Clinical Assistant Professor  
Department of Radiology  
University of North Carolina School of Medicine  
Chapel Hill, North Carolina

**Adriana Palade, MD**

Director of the Comprehensive Epilepsy Surgery Program  
Associate Professor of Neurology  
Department of Neurology  
West Virginia University  
Morgantown, West Virginia

**Edgar Perez, BA**

Duke University Medical Center  
Durham, North Carolina

**Jeffrey Petrella, MD**

Professor  
Division of Neuroradiology  
Department of Radiology  
Duke University Medical Center  
Durham, North Carolina

**Rodney A. Radtke, MD**

Professor, Department of Neurology  
Chief, Division of Epilepsy and Sleep  
Duke University Medical Center  
Durham, North Carolina

**Dinesh V. Raju, MD, PhD**

Neurologist  
Department of Neurology  
Gwinnett Clinic  
Lawrenceville, Georgia

**Candace Richardson, RD, LDN, CNSC**

Clinical Dietitian  
Department of Pediatrics  
Duke Children's Hospital  
Durham, North Carolina

**Sarah K. Rivelli, MD, FACP**

Assistant Professor, Departments of Psychiatry and  
Behavioral Sciences and Medicine  
Duke University School of Medicine  
Durham, North Carolina

**Phillip D. Ruppert, PhD**

Instructor  
Department of Neurology and Psychiatry  
Saint Louis University  
St. Louis, Missouri

**Elizabeth K. Ruzzo, PhD**

Postdoctoral scholar  
Semel Institute for Neuroscience and Human Behavior  
University of California, Los Angeles  
Los Angeles, California

**Pradeep Sahota, MD, FAAN, FAES, FANA,  
FACP, FAASM**

Professor and Chairman, Department of Neurology  
University of Missouri—School of Medicine  
University of Missouri Health Care;  
Attending Physician  
HST Memorial Veterans Hospital  
Columbia, Missouri

**Cesar C. Santos, MD**

Professor and Chief  
Division of Pediatric Neurology  
Department of Pediatrics  
MedStar Georgetown University Hospital  
Washington, DC

**Sandra Serafini, PhD**

Assistant Professor  
Division of Neurosurgery  
Department of Surgery  
Duke University Medical Center  
Durham, North Carolina

**Cheolsu Shin, MD**

Consultant in Neurology  
Chair, Section of Epilepsy  
Department of Neurology  
Mayo Clinic Rochester  
Rochester, Minnesota

**Rajdeep Singh, MD, MS**

Medical Director—Neurodiagnostics  
Neurosciences Institute—Neurology  
Carolinas Medical Center  
Charlotte, North Carolina;  
Clinical Assistant Professor of Neurology  
University of North Carolina School of Medicine  
Chapel Hill, North Carolina

**Saurabh R. Sinha, MD, PhD**

Associate Professor  
Department of Neurology  
Duke University Medical Center;  
Neurodiagnostic Center  
Veterans Administration Medical Center  
Durham, North Carolina

**Christa B. Swisher, MD**

Assistant Professor  
Department of Neurology  
Duke University Medical Center  
Durham, North Carolina

**Tung T. Tran, MD, MSc**

Assistant Professor  
Department of Neurology  
Duke University Medical Center;  
Director, Durham Epilepsy Center of Excellence  
Durham VA Medical Center  
Durham, North Carolina

**Amit Verma, MD**

Director, Division of Neurophysiology  
Director, Comprehensive Epilepsy Program  
Department of Neurology  
The Methodist Neurological Institute  
Houston, Texas

**Erick N. Viorritto, MD, MPH**

Neurologist

Division of Neurology

Department of Pediatrics

Nemours Children's Specialty Care;

Director

Pediatric Sleep Laboratory

Baptist Medical Center and Wolfson Children's Hospital

Jacksonville, Florida

**Terence Wong, MD, PhD**

Professor

Department of Radiology

Chief, Division of Nuclear Medicine

Director of Molecular Imaging and Medical Director,

Biomedical Research Imaging Center (BRIC)

Lineberger Comprehensive Cancer Center

University of North Carolina School of Medicine

Chapel Hill, North Carolina

# Preface

Epilepsy is one of the most common neurologic disorders, affecting more than 2 million Americans. The Institute of Medicine estimates that approximately 150,000 new cases of epilepsy are diagnosed each year in the U.S., and 1 in 26 people will develop this condition in their lifetime. In a recent report released by the American Academy of Neurology, Epilepsy remained the most popular subspecialty among U.S. neurologists, as it was in 2008. Recognizing epilepsy as a subspecialty within neurology, the Accreditation Council for Graduate Medical Education established epilepsy fellowships a few years ago. The American Board of Psychiatry and Neurology created a subspecialty in epilepsy exam to test competence in this field. Clearly, epilepsy is recognized as a common illness and many neurologists are interested in studying and specializing in it. Additionally, the study of epilepsy has an established educational curriculum and certifying examination. All this points to the need for resources to teach and learn about epilepsy.

Most neurology residency programs offer at least some training in epilepsy. Epilepsy and clinical neurophysiology fellowships provide much more in-depth education for those that want to subspecialize. Courses in epilepsy and EEG education are available through several national and international societies. However, there are few textbooks available for those interested in obtaining a well-rounded education in this discipline. Certainly, there are large comprehensive resources that serve as references. And there are other books that focus on specific issues in epilepsy. There is a paucity of books that provide a comprehensive yet concise review of the entire field that can be read easily by the trainee as well as someone interested in a more thorough understanding of the field.

With *Practical Epilepsy*, I hope to fill the gap in available epilepsy textbooks. It contains enough information to provide an excellent foundation for understanding epilepsy and is concise enough to be read cover-to-cover. For easy readability, it is divided into four sections: Clinical Aspects, Diagnostic Evaluation, Treatment, and Special Situations. Each section is written to provide a thorough, yet easy to read and understand synopsis of the relevant topic. Wherever possible, consistency is maintained between chapters so that the reader has a seamless experience while reading the text. In the Special Situations section, important topics that are often overlooked are discussed. This includes chapters

like Metabolic Epilepsies, Epilepsy and Headache, EMU Safety Concerns, among others.

Having been a clinical neurophysiology/epilepsy fellowship program director for many years, I always found it frustrating that I did not have a recommendation for new fellows when they asked which textbook they should buy to read during their fellowship. I always pointed them toward EEG textbooks since I could not identify an epilepsy text that they could read in its entirety. Hence, *Practical Epilepsy*. Fellows in epilepsy and clinical neurophysiology, neurology residents, and other trainees interested in epilepsy will find this book very useful. Because of how common epilepsy is, as noted at the outset, all neurology practitioners, if not all physicians, will find practical and useful information in this book presented in an easy to read and understand manner. Neurosurgeons and psychiatrists will find much that is pertinent to their practices. Psychologists, nurses, epilepsy/EEG technologists and others who care for patients with epilepsy will also find this book useful.

There are many people I must acknowledge, without whom this book would not have been possible. I have been incredibly fortunate to have been associated with the Duke Epilepsy Center for the last 20 years. The Duke Epilepsy Center has been treating patients and training physicians, nurses and technologists since the 1960s. It's association with the Durham Veterans Affairs (VA) Epilepsy Center (now called the Durham VA Epilepsy Center of Excellence (ECO)) has produced many leaders in the field. I have benefited from learning from many of them. The astute reader will recognize that all authors of this book have or have had an affiliation with Duke University. Many were staff neurologists, trainees or faculty in other departments. I am indebted to all these colleagues for taking time in their busy schedules to contribute chapters. None of what we do as epileptologists and clinical neurophysiologists can be possible without the incredible support of our nurses and technologists. The Duke Epilepsy Center and the Durham VA ECOE have been lucky to have the best! Our administrators, often not talked about, are also critical to our success. Without them, we could not do what we do. Of course, the most important are our patients. They inspire us with their stories, their motivation, their persistence, their courage, their perseverance, and their trust.

I must also acknowledge the wonderful support from Demos Medical Publishing. In particular, Beth Barry has been incredible to work with. She recognized the need for *Practical Epilepsy* and helped me formulate the concept for the book. Her encouragement and patience has been vital. Her associates, first Lee Oglesby and then Norman Graubart, have been very helpful in the administrative aspects of compiling this text. To all of them, I am incredibly grateful.

There are two people that I have tremendously neglected while editing this book—my wonderful sons,

Aamer and Aayaz. I hope to play more basketball with them now! Finally, nothing would be possible without the person to whom this book is dedicated, Sarwat Mohsin Husain, my wife. Words cannot express what I feel. She is the glue that not only holds our family together but also holds me together. To the three of them, all I can say is—thank you, ... and sorry.

*Aatif M. Husain, MD*

# **Practical Epilepsy**

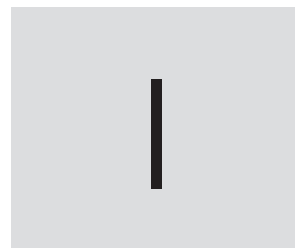




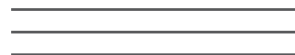
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## Practical Epilepsy





P A R T



# Clinical Aspects



# Pathophysiology

*Cheolsu Shin*

# 1

## CHAPTER

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The past decade has seen an explosion of the discovery of various genetic causes of many diseases, including epilepsy. With the rapid technological development in genomic sciences, many different approaches to finding genetic defects and variations underlying many disease states and epileptic conditions have been made available. The National Institutes of Health (NIH) supported a multicenter project to gather genomic and phenomic data on epileptic siblings or families that is expected to provide further rich soil for important discoveries. Furthermore, it seems that the time when individuals can have their entire genome sequenced for individualized management is approaching.

In this setting, the International League Against Epilepsy (ILAE) also proposed revised classification of seizures and epilepsies to incorporate the improved understanding of the pathophysiology of many seizures and epileptic conditions into the classification schemes (1). There have been many genetic defects and alterations identified that can lead to abnormal neuronal excitability. In some cases, it is easy to deduce the pathophysiology if the defect involves the molecular cascade underlying neuronal excitability. Ion channel or neurotransmitter receptor system abnormalities can easily be translated into abnormal physiology leading to an epileptic process. Other may not be that obvious, with seizure being the indirect result of the genetic abnormality. The bulk of the epileptic conditions still await further elucidation of their underlying pathophysiology.

There are two potentially separate processes that are involved in the epileptic brain. When a previously normal brain acquires the tendency for the occurrence of epileptic seizures, this is referred to as the epileptogenic process or epileptogenesis (2). When a seizure occurs in a brain that already possesses this tendency, this is referred to as an ictogenic process or ictogenesis (3). This may sound like a semantic argument, but there is ample experimental evidence that these two processes are different, although they may share some pathways and may also interact with and promote one another. Understanding the epileptogenic process may allow for early intervention in susceptible populations to prevent the eventual development of epilepsy.

Better understanding of the ictogenic process may lead to better pharmacological or physiological management of the existing epileptic brain.

Since neuronal excitability is based upon the actions of various receptors and ion channels that occur at the level of the neuronal membranes and synapses, it is easy to explain some of the epileptic conditions given known molecular genetic alterations (4). If there are changes in the ion channels (sodium, potassium, calcium, chloride, etc.), then the resulting hyperexcitability may be obvious. If the excitatory neurotransmitter receptor system is hyperactive, or if the inhibitory neurotransmitter system is hypoactive, then hyperexcitability would be the likely consequence. However, the neuronal network is not that simple, as there are complex connections, feedback loops, presynaptic versus postsynaptic actions, etc., so that hypoactivity of the excitatory system controlling the inhibitory circuit may result in hyperexcitability.

There are also obvious anatomic abnormalities that cause epilepsy, such as brain tumors, tuberous sclerosis complex (TSC), cavernous hemangioma, or cortical dysplasia. Removal of the anatomic lesion leads to the abolition of the seizures. How these anatomic abnormalities cause the epileptic condition has not been fully elucidated.

In addition, neurons do not exist in a vacuum. They are supported by glial cells and are surrounded by the systemic circulation, including the blood-brain barrier. The glia do not just passively provide structural support for the neuronal network. They actively participate in regulating neuronal excitability and the understanding of their role in epilepsy is improving (5).

Many epileptic conditions may also entail involvement of inflammatory mechanisms. Some of these conditions are obvious, as in acute cases of meningitis or encephalitis that cause symptomatic seizures. Others may be more chronic, as in Rasmussen's encephalitis. It is also likely that these inflammatory mechanisms are involved in seizure-induced brain injury and epileptogenesis. Recently, more awareness of the immune mechanism underlying some of the epileptic processes was made when autoimmune antibodies were

identified that are directed against neuronal tissues causing inflammatory reactions and epilepsy (6).

## CELLULAR PHYSIOLOGY

Epilepsy ultimately involves a neuronal population and as such is mechanistically based upon excitable membrane physiology. Neuronal excitability is based upon the regulation of ion channels that are selectively permeable to specific ions that make up the intracellular and extracellular milieu. Membrane voltage is determined by the Nernst equation that incorporates the conductances of the select ion channels.

$$V_m = \frac{RT}{F} \ln \left( \frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o} \right)$$

Because of the differential ionic concentrations between the intra- and extracellular spaces, each ion-selective channel will have an equilibrium potential (reversal potential) that balances the chemical gradient and the electrical gradient. Whichever ion channel is open will contribute to or dominate the membrane potential. When the potassium channel is open, the membrane will hyperpolarize. Sodium channel opening will lead to depolarization. Chloride channel opening will not change the resting membrane potential much, as its equilibrium potential is near the resting potential, but its opening will shunt the currents to reduce the depolarizing or hyperpolarizing force from other channel openings. Calcium channel opening provides a much stronger and longer depolarization force, by virtue of being a divalent cation with double the current of monovalent sodium ions and by having a much steeper concentration gradient than sodium. In addition, calcium ion can trigger many cascades of intracellular signaling that can lead to neuronal plasticity. These neuronal membrane ionic conductances would work only if the ionic milieu is maintained. Ionic pumps utilizing adenosine triphosphate (ATP) energy source (eg, Na/K ATPase) will restore the ionic concentration gradients, as the neuronal activity continually causes ion transfers across the membrane through ion channels.

Many of the neurotransmitter receptors may function as ion channels. The gamma-aminobutyric acid (GABA)-A receptor is a chloride ion channel with allosteric modulation by benzodiazepines and barbiturates. Therefore, GABA-A activation would be inhibitory by keeping the membrane potential near the resting membrane potential. However, in the special situation of the developing fetal brain, the ionic gradient is maintained in such a way that GABA-A activation may actually depolarize the membrane. The GABA-B receptor is a metabotropic receptor that is indirectly linked via a G-protein to the potassium channel, which hyperpolarizes the membrane. Excitatory amino acid receptors of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or kainate act as gates of sodium ions and therefore depolarize the postsynaptic membrane. The *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors are channels that

also allow calcium entry. They require not only the binding of glutamate, but also depolarization, usually provided by the activity of AMPA glutamate receptors. This provides for an intense synaptic activity, which in turn allows calcium entry that can then trigger steps leading to neuronal plasticity. When the activity is too intense, the system may break down and neuronal injury and subsequent epileptogenesis may ensue.

## GENETIC EPILEPSY

There are many epilepsy syndromes that have identified genetic defects. There are several varieties of syndromes now described, the review of which is beyond the scope of this chapter, but there are many reviews that describe the molecular details (7,8). Many of these defects have obvious relevance to the epileptic condition with molecular abnormalities in the system directly underlying neuronal excitability. Some of these mutations have been validated in experimental systems to be the likely direct cause for the epileptic condition. Other mutations are not always obviously related or validated. In addition, the genetic abnormalities do not always translate into a uniform phenomenon throughout the brain. In the past, it may have been a safe assumption that if the epileptic condition is genetically caused, it must be a generalized epileptic condition. It is now known that many genetically identified epilepsies are focal, as in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE; nicotinic cholinergic receptor defect) and autosomal dominant partial epilepsy with auditory features (ADPEAF; leucine-rich glioma inactivated 1 (LGI1) mutation). In severe myoclonic epilepsy of infancy (SMEI; Dravet's syndrome; SCN1A sodium channel mutation), there are cell-specific subunit expressions to GABAergic inhibitory neurons in the cortical and hippocampal regions, whereby loss of function in the sodium channel would lead to loss of inhibition and therefore hyperexcitability (9). Therefore, abnormal gene expression may be directed to an area of the brain and to a subpopulation of neurons, be it excitatory or inhibitory, and may underlie focal hyperexcitability, leading to focal epilepsy syndromes.

There are also many genetic conditions where epilepsy is a prominent feature of the disorder, such as TSC. Some genetic conditions cause neuronal migrational abnormalities that are then associated with epileptic processes (eg, bilateral periventricular nodular heterotopia syndrome with X-linked dominant mutation of filamin-1 gene). Understanding how epilepsy develops in these genetic conditions may also shed light on other epileptic processes.

In TSC, epilepsy is a prominent feature (10). Infantile spasms occur frequently in this condition and focal seizures may originate from the cortical tubers. In many cases, the seizures are refractory to medications. Resection of the cortical tubers identified as the focus of seizures frequently leads to many seizure-free years, thus implicating tuber formation in the pathogenesis of epilepsy (11). The TSC protein complex is a negative regulator of the mTOR signaling pathway, and

the TSC protein complex mutation leads to abnormal activation of this pathway. This leads to the formation of various tumors, including the subependymal giant cell astrocytoma (SEGA). Rapamycin inhibits the mTOR pathway and it has been shown to be effective in the treatment of SEGA. However, in the already established epileptic condition of TSC, rapamycin is not proven to be effective in controlling seizures. Since there is an overabundance of glia in the tuber along with giant cells, it is likely that the epileptogenesis occurs through mechanisms related to glial dysfunction. As discussed in the following sections, glial proliferation and abnormal glial morphology can lead to shrinkage of the extracellular space and reduced buffering capacity for potassium and glutamate, all promoting abnormal neuronal excitability in and around the cortical tubers.

### AUTOIMMUNE EPILEPSY

Recent report suggests that there may be another mechanism underlying epilepsy, especially drug-resistant epilepsy. Many epilepsy centers evaluate patients with pharmacoresistant epilepsy and evaluate them for a resective surgical option. In cases of normal high-resolution anatomic imaging, there may be a microscopic focus of abnormal circuitry. In these cases, functional imaging and invasive electrophysiology are used to locate the source of the epileptic process. However, there are many situations where there does not seem to be a good surgical solution.

At least in some of these cases, there may be additional pathophysiologic mechanisms to be considered. Seizures may occur in obvious cases of inflammatory processes, such as viral encephalitis, including herpes simplex encephalitis that preferentially affects the temporal lobes. Cerebritis related to systemic immune dysfunction, such as lupus, can be associated with seizures. Rasmussen's encephalitis that may involve a hemisphere, mostly in young people, is a well-known entity with likely participation of cell-mediated immune mechanisms. There are well-recognizable situations of paraneoplastic limbic encephalitis.

Nevertheless, there are patients who do not have any significant encephalopathy but have refractory seizures. In one study of these cases, neuronal autoantibodies were found mostly directed to voltage-gated potassium channel complex, glutamic acid decarboxylase (GAD) 65, collapsing response mediator protein (CRMP) 5,  $\alpha$ 5, NMDA-receptor, and neuronal nicotinic ganglionic acetylcholine receptor (6). There were imaging abnormalities, some of which were subtle and initially not noticed. A few patients had a neoplasm. Immunotherapy consisting of high-dose intravenous methylprednisolone, intravenous immunoglobulins, or combinations including plasma exchange or cyclophosphamide resulted in seizure freedom in two-thirds of the patients. Eight of 18 responders (44%) became seizure-free within 12 weeks of initiation of immunotherapy. This study raises many questions regarding a major subset of patients with pharmacoresistant epilepsy. In the appropriate clinical setting, it is important to consider

immunologic mechanisms as a cause of medical intractability. Eventually, controlled clinical trials and studies of basic immune mechanisms should lead to a more rational basis for alternative therapy options.

### ROLE OF ASTROGLIA IN EPILEPTOGENESIS

Although the final manifestation of epileptic seizures comes through as synchronized abnormal neuronal activity, the role of astroglia cannot be ignored. The glia is not just the supporting structural framework for the neuronal network, but it is an integral part of the homeostatic milieu that is necessary for neuronal integrity and function. Furthermore, there is active interaction between neurons and glia during normal neurotransmission. Any perturbation of these neuron–glial interactions leads to pathology, including hyperexcitability that may lead to epileptogenesis. In addition, the glia, along with the vasculature, forms the blood–brain barrier that insulates the brain from many systemic influences and insults. When the blood–brain barrier is disrupted, inflammation may ensue, and with all of its injurious components, the process of epileptogenesis may begin (12). Autoimmune epilepsy discussed earlier may well be an example of such a process.

Even focal epileptic conditions such as mesial temporal lobe epilepsy have been shown to have severe gliosis in the hippocampus, leading to terminology such as Ammon's horn sclerosis or mesial temporal sclerosis (MTS). Obviously, where there is excessive gliosis and absence of neuronal elements, seizures do not originate from that region. However, seizures may be triggered from the adjacent areas where the gliosis may be impacting neuronal function.

Since glia cells regulate the ionic milieu of neurons, they can alter neuronal excitability by affecting water flow and ionic buffering, including potassium. This can change the extracellular space and the ionic concentrations around the neurons. Shrinking the extracellular space will increase neuronal excitability due to higher extracellular potassium concentration and possible ephaptic neuronal synchronization. Hypo-osmolar situations (water intoxication or severe hyponatremia) swell the cells and thereby shrink the extracellular space, and these situations may cause seizures. Aquaporin-4, the glial water channel and the inward rectifying potassium channel (Kir) may be part of the glial control mechanism in this respect, and their dysfunction may lead to hyperexcitability (13).

Glia also take up glutamate released from the glutamatergic excitatory terminals to limit the spread of the neurotransmitter to extrasynaptic sites or adjacent synapses. In addition, glutamate released by the synapse can activate the glial metabotropic glutamate receptors that increase the glial intracellular calcium. This elevation of intracellular calcium then releases glutamate to the extracellular space. This constitutes bidirectional neuro–glial communication. Similar bidirectional communication may occur with other neurotransmitters. Whether this bidirectional communication is physiologically important is unknown. However, in

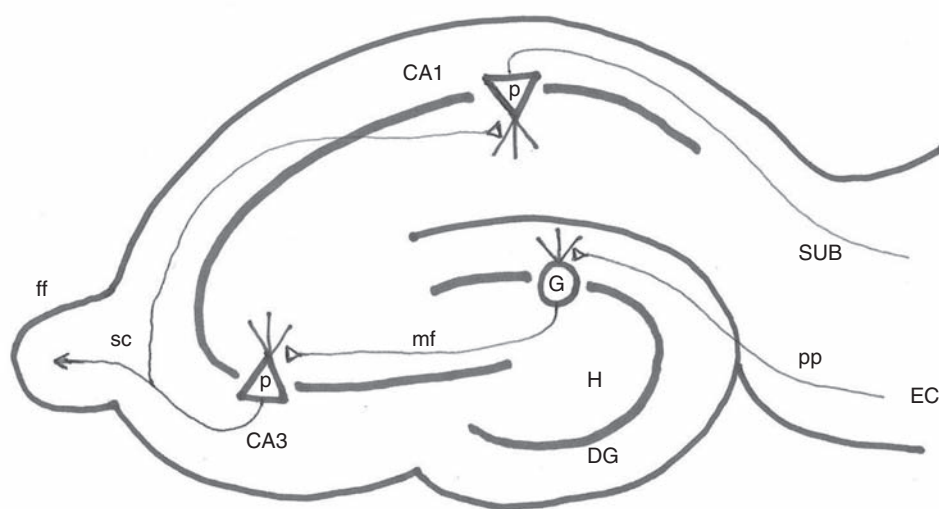


pathologic situations where glial proliferation takes place, the extracellular space may already be reduced, and glial release of glutamate may promote synchronized epileptic activity in the surrounding neuronal network, as evidenced by in vitro experiments (14).

The blood–brain barrier, along with the microvasculature of the brain, is formed by glia. Glia maintain the tight junctions between the endothelial cells and facilitate or filter the transfer of a variety of molecules from the systemic circulation to the brain parenchyma and vice versa. As such, glia would be part of any process that would allow immune system access to the brain parenchyma. In cases of autoimmune epilepsy, neuronal autoantibodies may be accessing the brain parenchyma, somehow via participation of the glia. In cases of injury to the brain, be it trauma, infection, or ischemic insult, there is reactive inflammation that seeks to repair the damage. Since so many complex cascades of microglial and other reactive elements participate in these repair processes, it may be very difficult to tease out which parts would end up promoting epileptogenesis. This endeavor at the basic science level may be critical in elucidating the mechanisms of epileptogenesis in acquired epileptic conditions, so that one can devise ways to intervene to prevent the development of epilepsy. There is accumulating evidence for the pathogenic role of glia underlying hyperexcitability in epilepsy through synchronizing glial neurotransmission, by controlling the extracellular space volume and ionic milieu, and participating in inflammatory processes (5).

## MESIAL TEMPORAL SCLEROSIS

The temporal lobe appears to be the most frequent anatomic site for epileptogenesis. In particular, the hippocampal formation and its surrounding structures of subiculum, entorhinal cortex, and parahippocampal gyrus appear to be particularly involved in the epileptic process in humans. Anatomic connections of the hippocampal circuitry are well known (Figure 1.1). The entorhinal cortex provides input to the dentate granule cells via the perforant path; dentate granule cells then innervate the CA3 pyramidal neurons via the mossy fibers. The CA3 pyramidal neurons innervate the CA1 pyramidal neurons via the Schaffer collaterals, and subsequently, CA1 pyramidal neurons provide output to the subiculum and through the fornix to the extrahippocampal areas. These synapses are excitatory and therefore may serve as an amplifier and, along with inhibitory interneurons, as a fine-tuning circuit for new memory formation. Because of the compact layers of neurons and ample excitatory synapses in these pathways, the hippocampus is one of the most susceptible structures in the brain for neuronal damage from a variety of insults (ischemic, traumatic, inflammatory) and from excessive seizure activity. As a result, the pathological entity of MTS has been well recognized and it is now more easily detected in vivo using high-resolution magnetic resonance imaging (MRI) scans. Many experimental models have been used to study the process of epileptogenesis in the hippocampus in vivo and in vitro, with much insight gained into the pathogenesis of epilepsy from this region of the brain (15).



**FIGURE 1.1** Schematics of Hippocampal Circuitry. Entorhinal cortex (EC) innervates the dentate granule cells (G) via the perforant path (pp). Granule cells send mossy fiber (mf) that innervates the CA3 pyramidal neurons (p). CA3 pyramidal neurons then send Schaffer collateral fibers (SC) that innervates CA1 pyramidal neurons, which in turn send fibers to subiculum (SUB) and thus completing the trisynaptic excitatory connections.

*Abbreviations:* Fimbria-fornix (ff); dentate gyrus (DG); dentate hilus (H)

Pathologically, the typical pattern is called Ammon's horn (Cornu Ammonis) sclerosis, where the CA subfields have a sparse population of pyramidal neurons with much glial proliferation, although the dentate gyrus, entorhinal cortex, and parahippocampal gyrus are also affected to a lesser extent. The pathology from experimental studies and human patients with mesial temporal sclerosis demonstrate a characteristic pattern of axon dysinnervation of the dentate granule cells, called mossy fiber sprouting. Instead of projecting normally to the CA3 subfields, the sprouting fibers turn back and innervate the granule cell layer and inner molecular layer of the dentate gyrus. This results in a recurrent excitatory loop that leads to hyperexcitability of the dentate granule cell population. Another hypothesis, the dormant basket cell hypothesis, proposes that it is the loss of inhibition that leads to hyperexcitability. Mossy cells in the hilus normally innervate the GABAergic basket cells that inhibit the dentate granule cells (16). Following an insult, be it status epilepticus, or head trauma, mossy cells also degenerate, leaving the inhibitory basket cells dormant, and hyperexcitability of the dentate granule cells ensues. It is possible that both recurrent excitation of the dentate granule cells and loss of inhibition of the basket cells contribute to epileptogenesis in MTS.

These epileptogenic processes appear to involve new synapse formation as part of plasticity of the brain, albeit maladaptive. Protein synthesis inhibition can curb mossy fiber sprouting and block epileptogenesis. Which molecular pathway is critical in mediating this maladaptive plasticity is obviously an area of active research in many laboratories. Of many potential molecules, brain-derived neurotrophic factor (BDNF) pathway may be a very promising candidate (17).

BDNF is one of many signaling molecules in the brain that triggers a cascade of intracellular events that underlie neuronal plasticity. It belongs to the nerve growth factor (NGF) family that promotes the survival of neurons and the growth of their neurites and processes. It binds to a receptor, TrkB, that phosphorylates tyrosine moieties in the protein, leading to activation of intracellular signaling cascades. In many animal models, seizures induce increased BDNF expression that promotes activation of its TrkB receptor in the mossy fiber pathway. Experimental manipulation of BDNF or TrkB expression and activation appear to have a profound effect on the development of the epileptic condition. If the BDNF/TrkB activity is increased, then the epileptogenic process is enhanced. If, on the other hand, the BDNF/TrkB expression is blocked, then the epileptogenic process is attenuated. This BDNF/TrkB pathway may provide an important avenue of clinical application aimed at blocking epileptogenesis in situations of brain injury that are highly likely to lead to epilepsy.

### PATHOPHYSIOLOGY OF PRIMARY GENERALIZED EPILEPSIES

Classic childhood absence seizures with 3 Hz spike and wave discharges have been better characterized in terms of pharmacology and pathophysiology than most other forms

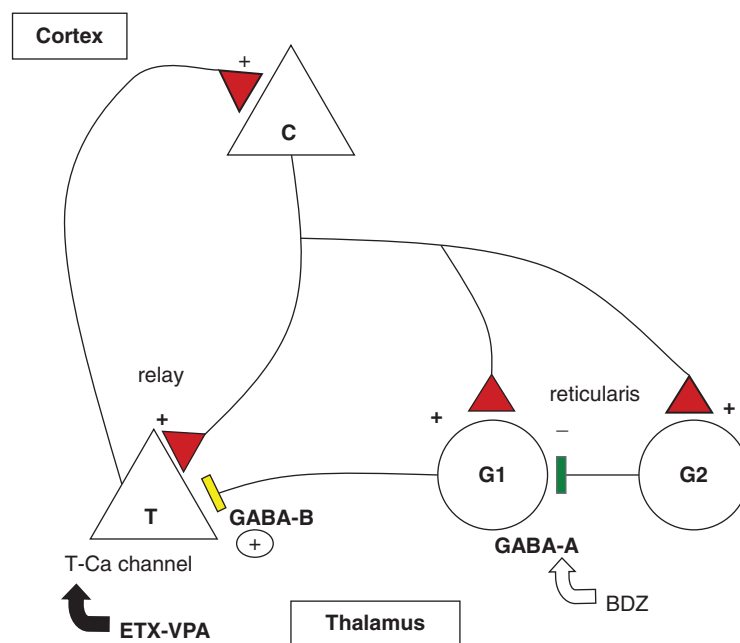
of epilepsy. Ethosuximide has been used as a very specific medication for this form of epilepsy with its T-calcium channel blocking activity identified as a mechanism of its antiepileptic property.

In terms of the network concept of epilepsy, the centrencephalic theory had been initially proposed with the reticular thalamus as the pacesetter. Subsequently, the corticoreticular theory postulated the involvement of the cortex in thalamocortical excitability. Some animal model studies suggest a cortical focus that entrains the cortex as well as the thalamus to generate self-sustaining spike wave discharges (18). Whether the animal model accurately predicts human absence epilepsy is unclear. Nevertheless, these studies suggest a basis for the absence epilepsy involving the cortex as well as the thalamus in a circuit that includes ion channels and neurotransmitter receptor systems that support the reverberating excitatory discharges (Figure 1.2).

The reverberating corticothalamic connections are modulated by the GABAergic innervation. GABA-B receptor activation on the thalamic relay neurons (T) provides the hyperpolarization needed for the de-inactivation of the T-calcium channel so that abnormal 3 Hz spike and wave discharges can be sustained. GABAergic interneurons (G2) may inhibit the GABA-B projection (G1) by GABA-A inhibition or may directly inhibit the relay neuron (T). Drugs effective in absence epilepsy, ethosuximide (ETX) and valproate (VPA), inhibit T-calcium channels. Benzodiazepines (BDZs) through the GABA-A mechanism.

As mentioned, the low threshold T-calcium channel is an integral part of the thalamocortical network communication (19). Its electrophysiological properties may explain some of the pharmacological effects of the GABA receptor system on absence seizures. T-calcium channels have a similar property to the voltage-gated sodium channels, in that once it is opened with depolarization, it becomes inactive and closed until it is de-inactivated. That de-inactivation requires a significant degree of hyperpolarization beyond the resting membrane potential. Many channels contribute to the return from depolarization, including the GABA-A receptor-coupled chloride channel. More recently, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have been implicated in the oscillation of thalamocortical circuitry (20). Like the T-calcium channel, the HCN channel is inactivated by depolarization and requires hyperpolarization for de-inactivation. Its reversal potential is  $-25$  to  $-40$  mV so that it may not provide the depolarization offered by the T-calcium channel, but may underlie the physiological as well as pathological oscillatory network behavior of the thalamocortical circuitry.

Thalamic relay neurons receive excitatory inputs from the cortex and may transmit a similar output back to the cortex, activating the T-calcium channel once. When the return volley of corticothalamic projections depolarizes the thalamic neuron, the T-calcium channels (and the HCN channels) are still in the inactive state, so that the oscillation is dampened and restrained in the physiological state. However, if there are hyperpolarizing inputs, that could change



**FIGURE 1.2** Functional anatomy of absence seizure. The reverberating corticothalamic connections are modulated by the GABAergic innervation. GABA-B receptor activation on the thalamic relay neurons (T) provides the hyperpolarization needed for the de-inactivation of the T-calcium channel so that abnormal 3 Hz spike and wave discharges would be sustained. GABAergic interneurons (G2) may inhibit the GABA-B projection (G1) by GABA-A inhibition or may directly inhibit the relay neuron (T). Drugs effective in absence epilepsy, ethosuximide (ETX) and valproate (VPA) inhibit T-calcium channels. Benzodiazepines (BDZ) would work through the GABA-A mechanism.

the delicate physiological balance. GABA neurons in the reticular thalamus also receive the cortical projections and in turn project to the relay neurons to modulate the activity. Although the GABA-A receptor function stabilizes the relay neurons, GABA-B receptors provide the hyperpolarizing force by activating the potassium channel that is linked to G-protein. In contrast to the GABA-A receptor-chloride channel with its reversal potential of  $-60$  mV, which is near the resting membrane potential, the potassium channel reversal potential is usually  $-80$  to  $-100$  mV, which allows de-inactivation of T-calcium channels, resetting them so that they are ready to open. Thus, the next corticothalamic volley will result in a powerful depolarizing force, leading to the reverberation of 3-Hz spike and wave discharges. Therefore, the pharmacological correlates of this circuitry would predict that attenuation of T-calcium channel activation would block the hyperexcitable reverberation, and indeed, ethosuximide and valproate, both T-calcium channel blockers, are effective against absence seizures.

It is also known that benzodiazepines that facilitate GABA-A receptor activation also block absence seizures. This action may be due to direct inhibition of both cortical and thalamic neurons, but it is also possible that GABAergic neurons in the reticular thalamus may also inhibit the GABAergic neurons that provide GABA-B projection to the thalamic relay neurons. As such, GABA-B antagonist in this scheme will be an effective antiabsence drug, whereas GABA-B agonist would more likely promote absence epilepsy.

## MECHANISM OF ICTOGENESIS

The discussion so far has mostly addressed how epilepsy develops in a previously normal brain, ie, epileptogenesis. This is a critically important issue to understand in order to prevent the occurrence of epilepsy. However, practically, it is important to manage the patients who already have gone through the process of epileptogenesis and are now having recurrent spontaneous unprovoked seizures. Of course, pharmacotherapeutics have come a long way since the past century with many new antiepileptic agents available and many new ones being investigated. These pharmacotherapeutics have been geared toward molecular targets of ion channels and neurotransmitter receptors, with agents that target sodium channels, potassium channels, GABA-A receptors, GABA transaminase inhibitors, and AMPA receptors.

More recent electrophysiological studies have shed light on a very interesting concept of how seizures start in the already epileptic brain (21). Newer understanding of this perspective may lead to novel therapeutic approaches, both pharmacologically and electrophysiologically. Ever since the EEG was discovered, the frequency range of brain electrical activity recorded has ranged between 1 Hz and 70 Hz, initially limited by the electronics of the amplifiers and the output of the tracings onto paper using an array of ink-pen printing mechanism. Now, in the presence of all digital EEG interface, there is no reason to be limited in frequency range in analyzing brain electrical activity. Experimental models of

epilepsy have already studied some of these high-frequency activities, and recent advances in digital electronics and computing power have enabled similar studies in humans who are undergoing epilepsy surgery in cases of medically refractory epilepsy.

There are many situations where the resection of a lesion, be it a tumor, cavernous hemangioma, or gliotic scar tissue, leads to seizure freedom in a previously refractory epileptic patient. In many cases, however, there has been no anatomic abnormality on neuroimaging studies with the need to resort to more invasive intracranial EEG monitoring in an effort to identify an epileptic focus for resection. Even then, it may not be possible to identify a focus, or resection of the putative focus may not achieve seizure freedom, leading to the conclusion that the epileptic focus was not fully resected.

In this setting, there is some emerging evidence that the identification of ultra-fast bursting activity (fast ripples) may represent the electrophysiologic biomarker for the epileptic focus. Resection of the brain regions with these discharges may lead to improved surgical outcome (22). These fast ripples, 250 Hz to 500 Hz bursting activity, have been recorded interictally during intraoperative electrocorticography and they seem to be present in the epileptogenic tissue. If the cortex where fast ripples are recorded is resected, seizure freedom is more likely. This finding was seen in a retrospective study with the need for further prospective studies to verify this hypothesis (22). This study has some weaknesses, but still may point toward an important direction for the future investigations (23).

The fast ripple is a pathological high-frequency oscillation (pHFO) that may indeed be a promising biomarker for localizing epileptogenic focus. As presented in reports from the conference on high-frequency oscillations (HFOs) in cognition and epilepsy (24), there is now much work ongoing in this field regarding normal and pathological significance of these high-frequency activities recorded from the brain, cortex, hippocampus, and subcortical structures. It appears that there are normal HFOs that occur in various brain areas, sometimes associated with different activities or states and at other times seemingly randomly. Underlying molecular and network mechanisms are beginning to be dissected. Whether the pHFOs contribute to the pathogenesis or are simply biomarkers of the epileptogenic zone or both is unclear. Regardless, this area of investigation holds great promise in furthering the understanding of molecular and circuit network behavior underlying the epileptic process.

There are neurons that physiologically fire repetitively in oscillation. It is hard to imagine, however, that a single neuron can be the starting focus of an epileptic process involving a large brain area with innumerable neurons. A network of pathologically active circuitry may be more likely the underlying process. In the thalamocortical reverberating circuitry, hyperactive low threshold calcium channel (T-calcium channel) could entrain the network into the epileptic population behavior of 3 Hz spike and wave discharges recorded using scalp EEG and resulting in the absence seizure. For focal seizures, there is no intrinsic reverberating circuitry that can

be entrained. However, in the injured area of the brain, or malformed or disorganized neuronal population, one may envision molecular and local alterations that may form the basis of some reverberation. Excitatory synapses that are hyperactive due to maladaptive plasticity may contribute. Also, ephaptic mechanisms may contribute in compact layers of neurons oriented in a single direction as in the hippocampus. Gap junctions may synchronize inhibitory neurons to hypersynchronize the network of bursting neurons. Gliosis and abnormal glial environment also contribute by shrinking the extracellular volume and reducing the buffering capacity for any spilled excitatory glutamate neurotransmitter and increased potassium ions. These all combine to form islets of small groups of neuronal circuits that may cause HFOs that are pathologic. These groups of small populations of neurons may not be able to launch an epileptic seizure on their own. But, given additional provocative factors, they could be recruited to synchronize in larger groups that may eventually be entrained to generate a clinical seizure phenomenon. Once a seizure is generated through the network, it may leave behind an engram that subsequent seizure events may follow to result in a stereotypic electrographic and behavioral epileptic pattern.

The pathophysiology of epilepsy is complex and encompasses diverse mechanisms and network connections. Although the basic science regarding the molecular mechanisms of neuronal excitability has advanced the understanding of epileptogenesis and ictogenesis, more research is needed to improve the understanding of these mechanisms (25). Ultimately, the epileptic condition is a human condition with much more than just hyperexcitable networks and abnormal molecular interactions. Hopefully, with better understanding of the science of epilepsy, it will be possible to deliver better care for the patients and the families with epilepsy.

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# Genetics

*Elizabeth K. Ruzzo, Rodney A. Radtke,  
David B. Goldstein, and Erin L. Heinzen*

## 2

C H A P T E R

Epilepsy is one of the most common neurological disorders, affecting ~3% of the human population at some period of life, with children and the elderly having the highest incidences (1). Epilepsy is a heterogeneous disorder made up of many (over 50 (2)) unique epilepsy syndromes and non-syndromic cases. Though epilepsy has diverse etiologies, it is highly heritable and genetics play an important etiological role. A number of different lines of epidemiological evidence support this claim, including higher concordance rates in monozygotic (49%) than in dizygotic (16%) twins (3) and increased risk in first-degree relatives of probands (4–6).

Epilepsy can be broadly classified by the suspected etiology: structural–metabolic (7) (previously known as symptomatic) cases are explained by brain malformations, tumors, strokes, or other detectable phenotypes; unknown (7) (previously known as cryptogenic) cases are suspected to be explained by a clinical neurological abnormality but the cause has not been identified; and finally, genetic (7) (previously known as idiopathic) cases have no obvious cause, but are presumably genetic. Approximately 30% of all epilepsies are considered to be idiopathic and thus likely to have a genetic basis (8). Idiopathic generalized epilepsies (IGEs) have an especially strong genetic component, with ~80% concordance for monozygotic twins (9); partial epilepsies, in contrast, have a monozygotic twin concordance of 36% (9). In fact, the International League Against Epilepsy (ILAE) Commission on Classification and Terminology now refers to these cases as genetic generalized epilepsy (GGE) (7). To complicate matters further, there is evidence that some structural–metabolic cases may also have underlying genetic factors that interact with environmental factors to increase disease susceptibility (10).

Diseases explained by simple monogenic Mendelian patterns of inheritance are rare compared to complex disorders that violate Mendelian inheritance. Complex disorders are caused by interplay between genetic and environmental factors. Epilepsy is a complex disorder; however, a very small proportion of epilepsy cases, roughly 1%, show genetic transmission in a Mendelian pattern. A majority of epilepsy cases

are either sporadic, with no known family history, or cluster in families that do not show a clear-cut pattern of inheritance.

## OVERVIEW OF THE HUMAN GENOME

### Basic Human Genetics

Deoxyribonucleic acid, or DNA, is the hereditary material in humans and almost all other living organisms. DNA is made up of four unique chemical bases, or nucleotides, including: adenine (A), cytosine (C), guanine (G), and thymine (T). This alphabet of nucleotides provides instructions for sequences of amino acids (three nucleotide combinations code for each of 20 amino acids), which the body uses to build proteins – the workhorses of the cell. A segment of DNA that codes for a protein is called a gene. The central dogma of biology states that a gene is transcribed into a messenger ribonucleic acid (mRNA) transcript, which is then translated into a protein. Before the final mRNA is translated into protein, the pre-mRNA transcript contains both introns and exons. Introns are removed from the transcript and the exons are the portion of the gene that gets directly translated into protein.

The human genome consists of three billion base pairs of DNA and ~20,000 genes. The proportion of the human genome that is protein-coding (“the exome”) is very small, accounting for less than 2% of the genome. The remaining 98% of the genome, noncoding DNA, is not used to encode proteins. We do not fully understand the function of all noncoding DNA, however, some of it encodes RNA molecules with important biological functions (an exception to the central dogma) and other regions have important roles in regulating the expression of genes (how much gene product is available to a cell).

DNA usually exists as double-stranded DNA in which Watson–Crick base pairs (guanine-cytosine and adenine-thymine pairing via hydrogen bonds) create a regular helical structure with a sugar phosphate backbone. This double helix enables the cell to easily copy the DNA molecule during cell division, enabling precise replication of our genetic material. The DNA double helix is further organized into 23 chromosomes: 22 autosomes (1–22) and the sex chromosomes (X or

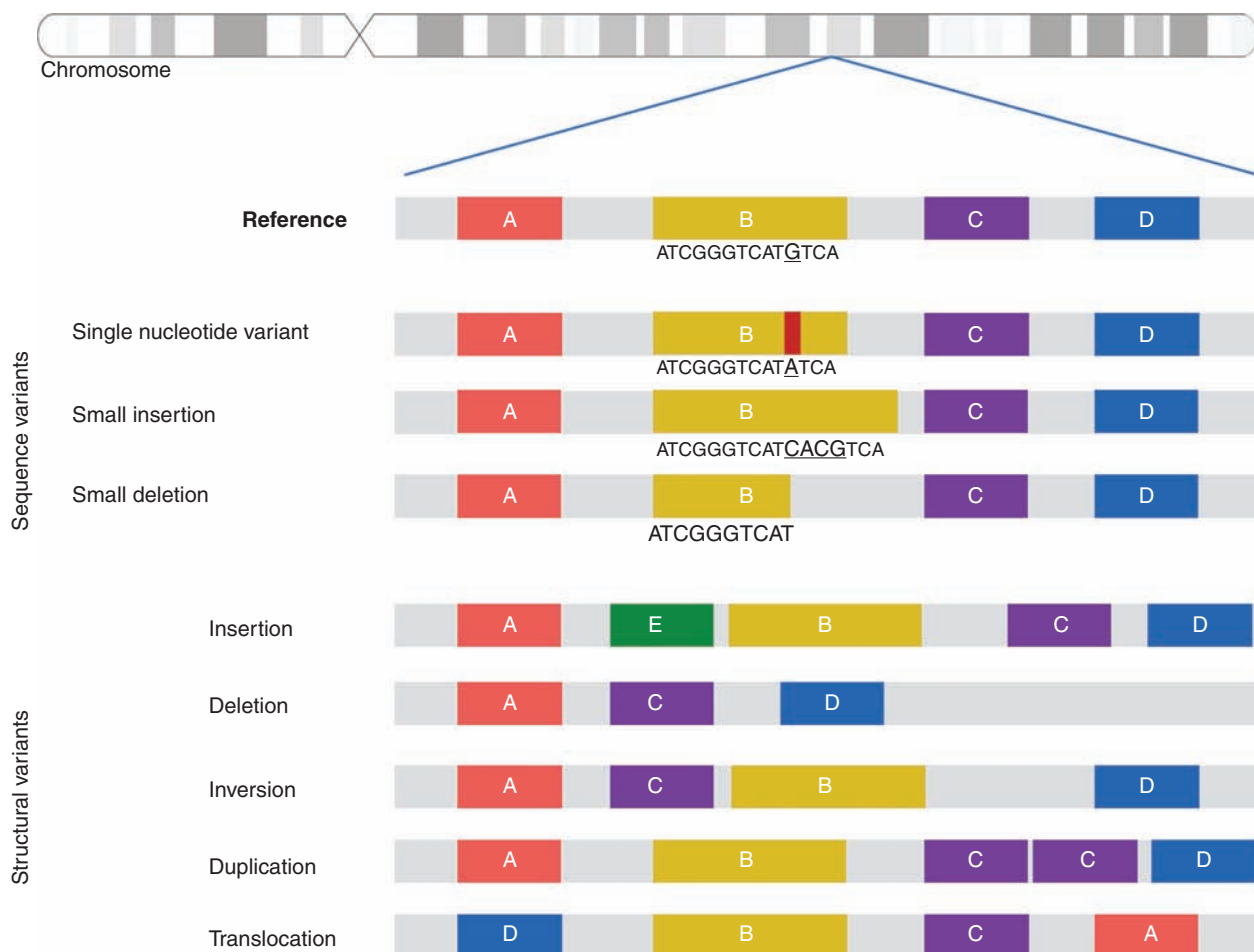
Y). The human sex cells (female ova and male sperm) are haploid, meaning they contain a single copy of our genome (three billion base pairs on 23 chromosomes). Importantly, the other ~50 trillion cells in our body are diploid, meaning they have two copies of the human genome—one inherited from our mother and the other from our father. Each human diploid cell has 6 billion base pairs of DNA, and without additional modification, this DNA would be 2 meters in length. DNA is further condensed to form chromatin. DNA wraps around proteins called histones creating a series of nucleosomes (nine histone proteins + 166 base pairs of DNA) with intervening “linker DNA” of ~20 base pairs; when viewed with an electron microscope, this gives the appearance of beads on a string. Thus, nucleosomes are the structural unit of chromatin and further coiling generates tightly compacted higher-order structures. Chromosomes are most highly compacted during metaphase (a phase in mitosis of the cell cycle) and metaphase chromosomes can be viewed under a light microscope.

Finally, in addition to the chromosomal genomic DNA (gDNA), which resides in the nucleus of the cell, humans also harbor a small amount of mitochondrial DNA (mtDNA). As suggested by the name, this DNA resides in the mitochondria of the cell. Mitochondria produce energy for the cell and

humans have hundreds to thousands of mitochondria per cell. Mitochondrial DNA contains 37 genes, packaged in a single circular chromosome; mtDNA is maternally inherited.

### Genetic Variation in the Human Genome

When we compare the human genome to that of our closest living relatives, the chimpanzees, we see differences in only ~1% of our genomes. When we compare the genomes of human individuals, we are ~99.9% identical. So why are individuals so unique? One of the main reasons comes from genetic variation. Even that 0.1% difference means we have many different changes in our genomes. In our 3 billion base pair genome, we have ~3.5 million sites (11) (or loci) where there is a single base pair change; these sites are different from the reference genome and are known as single nucleotide variants (SNVs). Some SNVs explain differences in our physical features, others are related to disease or drug responses (see the section Pharmacogenetics), but the majority of SNVs have no known phenotypic consequences. In addition to SNVs, there are other types of genetic variation, including small insertions or deletions (indels), copy number variants (CNVs), and larger structural variants (Figure 2.1).



**FIGURE 2.1** Types of variation in the human genome.



Each genetic variant is found at a certain frequency in the human population, with different subpopulations/ethnicities often having different frequencies for the same variant (population stratification). Typically, this frequency is described by the minor allele frequency (MAF). The MAF for a variant locus is between 0 and 50% and reflects the proportion of alleles (in the population) that are the less frequent allele (the “variant” allele). If a genetic variant is variable within or between populations, it is considered a genetic polymorphism (in contrast, genetic variants can be private). Therefore, a common single nucleotide variant is also known as a single nucleotide polymorphism (SNP). Genetic variants with different frequencies are detectable using different technologies and have unique implications for genetic analyses (Table 2.1).

## OVERVIEW OF DISCOVERY GENETICS IN EPILEPSY

The initial efforts to identify genes influencing epilepsy risk came from linkage studies in rare epilepsy families with Mendelian inheritance patterns. These familial linkage studies identified over 20 “epilepsy genes” (12); however, mutations in these genes only account for an estimated 1% of epilepsy cases (see the section Early Epilepsy Genetics and Known Epilepsy Genes). This highlighted the difficulties associated with genetic discovery in a clinically and genetically heterogeneous disorder, such as epilepsy.

The next efforts came from candidate gene, and later, genome-wide association (GWA) studies. Association studies were promising because, unlike linkage analyses that rely on acquisition of multiplex families, they could be conducted in case-control populations by comparing the frequency distribution of a variant(s). The candidate gene association studies were underpowered and no convincing susceptibility genes were identified using this approach (13) (see the section Candidate Gene Association Studies in Epilepsy). Three GWA studies, completed to date, provided only modest evidence for additional loci, and replication of these signals is

needed to prove their true association with epilepsy (see the section Genome-Wide Association Studies in Epilepsy).

Despite these abundant research efforts, scientists cannot explain the genetic basis of epilepsy in the vast majority of patients. The failure of association studies to discover common disease-associated variants lends credence to a rare variant-common disease model for epilepsy (14,15). Recently, the role of rare variation in human disease has become increasingly clear, especially the role of rare CNVs in neuropsychiatric disorders and epilepsy in particular (16–21) (see the section The Role of Copy Number Variants in Epilepsy). Current efforts are focused on the use of next-generation sequencing to systematically explore the role of rare variation in epilepsy (see the section Next-Generation Sequencing Studies).

Over one hundred genes have been associated with epilepsy (<http://www.epigad.org>; February 2014); however, the number of securely established genes is closer to 50 (Table 2.2).

## Early Epilepsy Genetics and Known Epilepsy Genes

Epilepsies appearing in multiplex pedigrees with Mendelian patterns of inheritance facilitated the first genetic discoveries in epilepsy and informed our understanding of the underlying biology of seizures. In 1995, the first epilepsy-associated gene was identified in families with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (22). By studying one large ADNFLE family, a region of interest was initially identified on chromosome 20 and, subsequently, this candidate region was narrowed to a single causal missense mutation in *CHRNA4*, encoding the cholinergic receptor, nicotinic, alpha 4. This process is called linkage analysis, and this is a traditional technique for identifying a candidate region for a gene associated with a given disorder.

Linkage analysis makes use of crossovers, or recombination events, that occur naturally during meiosis. Linkage analysis is conducted in either a single large pedigree or across multiple smaller pedigrees with identical phenotypes. Polymorphic genetic markers (eg, SNPs or microsatellites)

**TABLE 2.1** Frequencies of Variants in the Human Population

VARIANT CATEGORY	MINOR ALLELE FREQUENCY (MAF)	IMPLICATIONS FOR GENETIC ANALYSES
Common	5–50%	Used in traditional GWA studies
Less Common	1–5%	Variants catalogued more recently and included in the newest GWA chips for association testing
Rare	Less than 1% but polymorphic in one or more major human populations	Detectable by NGS and amenable to analysis strategies outlined in the section Next-Generation Sequencing Study Designs
Private	Much less than 1% and found only in a single or a handful of analyzed samples and their immediate relatives	Difficult to gather statistical evidence except through co-segregation in families

Source: Adapted from Ref. (81). Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. *Nat Rev Genet.* 2010;11(6):415–425.

TABLE 2.2 Epilepsy Genes and Their Associated Syndromes\*

GENE SYMBOL	GENE DESCRIPTION	CYTOGENETIC LOCATION	ASSOCIATED EPILEPSY PHENOTYPE(S)	MIM NUMBER(S)	MODE OF INHERITANCE
ARX	Aristaless-related homeobox, X-linked	Xp21.3	Epileptic encephalopathy, early infantile, 1	308350	XR
CDKL5	Cyclin-dependent kinase-like 5	Xp22.13	Epileptic encephalopathy, early infantile, 2	300672	XD
CHRNA2	Cholinergic receptor, nicotinic, alpha polypeptide-2	8p21.2	Epilepsy, nocturnal frontal lobe, type 4	610353	AD
CHRNA4	Cholinergic receptor, nicotinic, alpha polypeptide-4	20q13.33	Epilepsy, nocturnal frontal lobe, 1	600513	AD
CHRNB2	Cholinergic receptor, nicotinic, beta polypeptide-2	1q21.3	Epilepsy, nocturnal frontal lobe, 3	605375	AD
GABRG2	Gamma-aminobutyric acid (GABA) A receptor, gamma-2	5q34	Epilepsy, generalized, with febrile seizures plus, type 3; Febrile seizures, familial, 8	611277; 611277	AD; AD
KCNMA1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (slowpoke, Drosophila, homolog of)	10q22.3	Generalized epilepsy and paroxysmal dyskinesia	609446	AD
KCNQ2	Potassium voltage-gated channel, KQT-like subfamily, member 2	20q13.33	Seizures, benign neonatal, 1; Epileptic encephalopathy, early infantile, 7	121200; 613720	AD; AD
KCNQ3	Potassium voltage-gated channel, KQT-like subfamily, member 3	8q24.22	Seizures, benign neonatal, type 2	121201	AD
LGI1	Leucine-rich gene, glioma-inactivated, 1	10q23.33	Epilepsy, familial temporal lobe, 1	600512	AD
PCDH19	Protocadherin 19	Xq22.1	Epileptic encephalopathy, early infantile, 9	300088	X
SCN1A	Sodium channel, voltage-gated, type I, alpha polypeptide	2q24.3	Epilepsy, generalized, with febrile seizures plus, type 2	604403	AD
SCN1B	Sodium channel, voltage-gated, type I, beta polypeptide	19q13.12	Epilepsy, generalized, with febrile seizures plus, type 1	604233	AD
SCN2A	Sodium channel, voltage-gated, type II, alpha subunit	2q24.3	Seizures, benign familial infantile, 3; Epileptic encephalopathy, early infantile, 11	607745; 613721	AD; AD
SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	1p34.2	GLUT1 deficiency syndrome 1; GLUT1 deficiency syndrome 2	606777; 612126	AD; AD
STXBP1	Syntaxin-binding protein 1	9q34.11	Epileptic encephalopathy, early infantile, 4	612164	AD
ALDH7A1	Aldehyde dehydrogenase 7 family, member A1	5q23.2	Epilepsy, pyridoxine-dependent	266100	AR
ALG13	Alg13, S. cerevisiae, homolog of	Xq23	Epileptic encephalopathy (not in OMIM yet) (58)	N/A	XD
ARHGEF9	Rho guanine nucleotide exchange factor 9	Xq11.1-q11.2	Epileptic encephalopathy, early infantile, 8	300607	XR
ASAH1	N-acylsphingosine amidohydrolase (acid ceramidase) 1	8p22	Spinal muscular atrophy with progressive myoclonic epilepsy	159950	AR
CHD2	Chromodomain helicase DNA binding protein-2	15q26.1	Epileptic encephalopathy, childhood-onset	615369	AD
CLN8	CLN8 gene	8p23.3	Northern epilepsy variant	610003	AR

TABLE 2.2 Epilepsy Genes and Their Associated Syndromes\* (continued)

GENE SYMBOL	GENE DESCRIPTION	CYTOGENETIC LOCATION	ASSOCIATED EPILEPSY PHENOTYPE(S)	MIM NUMBER(S)	MODE OF INHERITANCE
CNTNAP2	Contactin-associated protein-like 2	7q35-q36	Cortical dysplasia-focal epilepsy syndrome	610042	AR
CPA6	Carboxypeptidase A6	8q13.2	Epilepsy, familial temporal lobe, 5; Febrile seizures, familial, 11	614417; 614418	AD; AR
CSTB	Cystatin B (stefin B)	21q22.3	Epilepsy, progressive myoclonic 1A (Unverricht and Lundborg)	254800	AR
DEPDC5	DEP domain-containing protein 5	22q12.2-q12.3	Epilepsy, familial focal, with variable foci	604364	AD
DNM1	Dynamin 1	9q34.11	Epileptic encephalopathy, early infantile, 31	616346	AD
EPM2A	Laforin	6q24.3	Epilepsy, progressive myoclonic 2A (Lafora)	254780	AR
GABRB3	Gamma-aminobutyric acid (GABA) A receptor, beta-3	15q12	Epileptic encephalopathy (not in OMIM yet) (58)	N/A	AD
GNAO1	Guanine nucleotide-binding protein (G protein), alpha-activating activity	16q12.2	Epileptic encephalopathy, early infantile, 17	615473	AD
GOSR2	Golgi snap receptor complex member 2	17q21.32	Epilepsy, progressive myoclonic 6	614018	AR
GRIN2A	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16p13.2	Epilepsy, focal, with speech disorder and with or without mental retardation	245570	AD
IER3IP1	Immediate-early response 3-interacting protein 1	18q21.1	Microcephaly, epilepsy, and diabetes syndrome	614231	AR
KCNT1	Potassium channel, subfamily T, member 1	9q34.3	Epileptic encephalopathy, early infantile, 14; Epilepsy, nocturnal frontal lobe, 5	614959; 615005	AD; AD
KCTD7	Potassium channel tetramerization domain containing 7	7q11.21	Epilepsy, progressive myoclonic 3, with or without intracellular inclusions	611726	AR
MEF2C	MADS box transcription enhancer factor 2, polypeptide C (myocyte enhancer factor 2C)	5q14.3	Mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations	613443	AD
NHLRC1	NHL repeat-containing 1 gene (malin)	6p22.3	Epilepsy, progressive myoclonic 2B (Lafora)	254780	AR
PLCB1	Phospholipase C, beta-1	20p12.3	Epileptic encephalopathy, early infantile, 12	613722	AR
PNKP	Polynucleotide kinase 3' phosphatase	19q13.33	Epileptic encephalopathy, early infantile, 10	613402	AR
PRICKLE1	Prickle-like 1	12q12	Epilepsy, progressive myoclonic 1B	612437	AR
PRICKLE2	Prickle-like 2	3p14.1	Epilepsy, progressive myoclonic 5	613832	AD
PRRT2	Proline-rich transmembrane protein 2	16p11.2	Seizures, benign familial infantile, 2; Convulsions, familial infantile, with paroxysmal choreoathetosis	605751; 602066	AD; AD
SCARB2	Scavenger receptor class B, member 2	4q21.1	Epilepsy, progressive myoclonic 4, with or without renal failure	254900	AR
SCN8A	Sodium channel, voltage gated, type VIII, alpha polypeptide	12q13.13	Epileptic encephalopathy, early infantile, 13	614558	AD

(continued)

TABLE 2.2 Epilepsy Genes and Their Associated Syndromes\* (continued)

GENE SYMBOL	GENE DESCRIPTION	CYTOGENETIC LOCATION	ASSOCIATED EPILEPSY PHENOTYPE(S)	MIM NUMBER(S)	MODE OF INHERITANCE
SCN9A	Sodium channel, voltage-gated, type IX, alpha subunit	2q24.3	Febrile seizures, familial, 3B; Epilepsy, generalized, with febrile seizures plus, type 7	613863; 613863	AD; AD
SIAT9	Sialyltransferase 9	2p11.2	Amish infantile epilepsy syndrome	609056	AR
SLC25A22	Solute carrier family 25 (mitochondrial carrier, glutamate), member 22	11p15.5	Epileptic encephalopathy, early infantile, 3	609304	AR
SNIP1	SMAD nuclear interacting protein 1	1p34.3	Psychomotor retardation, epilepsy, and craniofacial dysmorphism	614501	AR
SPTAN1	Spectrin, alpha, nonerythrocytic-1 (alpha-fodrin)	9q34.11	Epileptic encephalopathy, early infantile, 5	613477	AD
SRPX2	SUSHI repeat-containing protein, X-linked, 2	Xq22.1	Rolandic epilepsy, mental retardation, and speech dyspraxia	300643	X
ST3GAL3	ST3 beta-galactoside alpha-2,3-sialyltransferase 3	1p34.1	Mental retardation, autosomal recessive 12; Epileptic encephalopathy, early infantile, 15	611090; 615006	AR; AR
STRADA	STE20-related kinase adaptor alpha	17q23.3	Polyhydramnios, megalencephaly, and symptomatic epilepsy	611087	AR
SYN1	Synapsin I	Xp11.23	Epilepsy, X-linked, with variable learning disabilities and behavior disorders	300491	X
SYNGAP1	Synaptic Ras GTPase activating protein 1	6p21.32	Epileptic encephalopathy (not in OMIM yet) (27)	N/A	AD
SZT2	Seizure threshold 2, mouse, homolog of	1p34.2	Epileptic encephalopathy, early infantile, 18	615476	AR
TBC1D24	TBC1 domain family, member 24	16p13.3	Myoclonic epilepsy, infantile, familial; Epileptic encephalopathy, early infantile, 16	605021; 615338	AR

\*This list makes use of the Online Mendelian Inheritance in Man (OMIM) resource (<http://omim.org>). This list was generated from searching the OMIM gene map for phenotypes, including the words "epilepsy," "epileptic," or "seizure" and filtered to exclude associations with weak supporting evidence. This database is updated regularly and thus this table is based on findings as of January 21, 2014. In addition, several recent discoveries have not been entered into OMIM yet, but are included with the relevant publication listed. The most well-accepted and validated genes with a major effect on susceptibility Mendelian idiopathic epilepsies are listed in bold (82). AD: autosomal dominant; AR: autosomal recessive; XD: X-linked dominant; XR: X-linked recessive; X: X-linked female only (PCDH19 is associated with female-restricted epilepsy) or X-linked but mode of inheritance unclear from OMIM reports.

distributed throughout the genome are then genotyped in all individuals of the family. If the affected individuals in a pedigree nearly always inherit a genetic marker, then the disease gene and the marker are likely to be close together on the chromosome. Each marker can then be tested for co-segregation with the disease phenotype and the disease can be statistically “linked” to a specific region of the genome. In linkage analysis, a logarithm of odds (LOD) score compares the likelihood of obtaining the observed data if the tested loci are indeed linked to the likelihood of observing the same data purely by chance. If two genetic markers are on different chromosomes, then there is a 50-50 chance that they are inherited together and thus they are “unlinked.” In contrast, two genetic markers that are close together on the same chromosome have a high chance of being inherited together (“linked”), since it is less likely they will be separated by a meiotic recombination event. Thus, in linkage analysis, a “linked” marker has a high LOD score, indicating that very few meiotic recombination events have occurred between this marker and the disease gene, thus highlighting a chromosomal region of interest.

Once the candidate genetic region is mapped, the position of the disease-associated gene can be located on the chromosome through isolation of partially overlapping DNA segments that progress along the chromosome toward the disease gene, a technique referred to as positional cloning. Today, fine mapping can instead be achieved by referring to the human reference genome and subsequently sequencing (all genes or just candidate genes) within this linkage “peak” to directly identify the causal allele. Positional cloning in conjunction with family-based linkage mapping and analysis can work for gene identification even without knowledge of the biochemical nature of a disease, as was the case for the epilepsy studies in the late 1990s.

The earliest epilepsy genes fell into several main categories of voltage-gated or ligand-gated ion channels, namely subunits of acetylcholine receptors (*CHRNA2*, *CHRNA4*, and *CHRNA2*), subunits of sodium channels (*SCN1A*, *SCN1B*, and *SCN2A*), subunits of potassium channels (*KCNQ2* and *KCNQ3*), and subunits of gamma-aminobutyric acid (GABA) receptors (*GABRA1* and *GABRG2*). This led to the perception that epilepsy was primarily a “channelopathy,” resulting from disruption of normal electrical transmission between neurons.

While these classes of genes are still central to epileptogenesis, additional research has identified many new classes of genes (Table 2.2) highlighting the need to reconsider our narrow view of the properties of epilepsy genes. A diversity of examples exist, including: (i) leucine-rich, glioma-inactivated 1 gene (*LGII*) (23), a synaptic protein that may also regulate voltage-gated potassium channels (ii) disheveled, Egl-10 and Pleckstrin (DEP) domain-containing protein 5 (*DEPDC5*) of unknown function (24,25) (iii) Proline-Rich Transmembrane Protein 2 (*PRRT2*), also of unknown function (26) and (iv) Chromodomain Helicase DNA Binding Protein 2 (*CHD2*) (27), a chromatin remodeling protein.

In total, linkage studies in these Mendelian epilepsy families identified over 20 “epilepsy genes” (12) (Table 2.2).

Collectively, these genes explain only an estimated 1% of epilepsy cases. A majority of unsolved epilepsy cases are considered complex epilepsies, which will be explained by some combination of gene–gene or gene–environment interactions. It is also likely that the extent of genetic heterogeneity in the complex epilepsies will be greater than that of the Mendelian epilepsies, which would mean that many different genes would each explain only a very small proportion of epilepsy cases, making them evasive to current genetic approaches.

### Locus Heterogeneity and Variable Expressivity

Epilepsy shows extreme genetic heterogeneity. Locus heterogeneity is evident from the relatively large number of already established epilepsy genes. A single epilepsy syndrome may be caused by mutations in one gene in family A and caused by mutations in a different gene in family B. For example, Genetic Epilepsy with Febrile Seizures Plus (GEFS+) can be caused by mutations in *SCN1A*, *SCN2A*, *SCN1B*, or *GABRG2*. Variable expressivity is also observed in epilepsy; this is when mutations in a single gene can produce different epilepsy phenotypes in different individuals. For example, mutations in *SCN1A* can cause GEFS+ or Dravet syndrome. Until we have fully characterized all genotype–phenotype relationships, it will be difficult to understand the shared and distinct genetic influences on different epilepsy syndromes.

### Syndromes With Epilepsy as a Feature

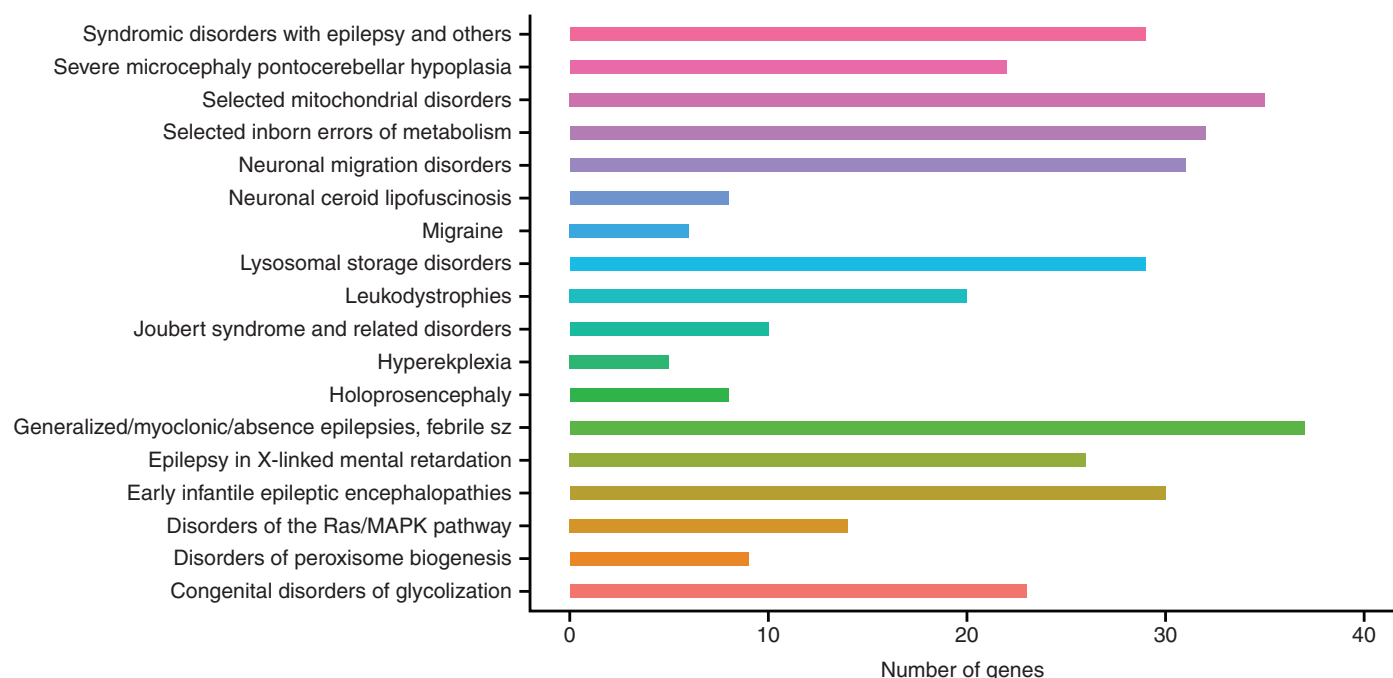
There are two broad categories of genes associated with epilepsy: those discovered in primary epilepsy syndromes and those discovered in syndromes with epilepsy as a feature (eg, brain development disorders). Genes in the latter category have also primarily been identified by linkage analyses. Both categories still inform the biological mechanisms of epileptogenesis and provide possible therapeutic targets.

Clinically, the presentation of these syndromic and non-syndromic phenotypes often confounds obtaining a clear diagnosis. In addition, determining the genetic basis of a patient’s epilepsy may help guide treatment and inform counseling of recurrence risk. To aid in genetic diagnoses for epilepsy, a panel of 265 genes that are “most relevant” to epilepsy have been recommended for genetic testing (28). This includes 18 phenotypic groupings or subpanels (Figure 2.2). Sequencing these 265 genes in 33 epileptic patients resulted in the identification of a presumably causal variant in 48% of patients ( $n = 16$ ) (28). In addition to acting as a diagnostic tool, use of this targeted sequencing panel will also uncover the phenotypic heterogeneity associated with the less frequently mutated genes.

### GENETIC ASSOCIATION STUDIES

Association studies seek to determine if two things occur together more often than expected by chance. In a classical





**FIGURE 2.2** A bar graph of the recommended genes for NGS diagnosis in epilepsy patients categorized by phenotypic grouping/subpanel. This includes 324 unique genes; including 280 genes in one phenotypic group, 38 genes in two phenotypic groups, and 6 genes in three phenotypic groups.

Source: From Ref. (28). Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. *Epilepsia*. 2012;53(8):1387–1398.

genetic association study, these “things” are (a) a single-locus allele or genotype and (b) a phenotype (disease cases vs. healthy controls). In other words, genetic association studies can identify genetic variants that are associated with a disease or trait. If a genetic association increases susceptibility to a given disease, then the associated genetic variant will be seen more often than expected by chance in diseased individuals. While this sounds simple enough, there are many critical methodology issues to consider when conducting association studies; and true genetic associations are the result of carefully conducted studies involving large cohorts, replication cohorts, and statistically robust methods (13,29).

### Candidate Gene Association Studies in Epilepsy

Before genome-wide approaches to association studies were readily accessible, many scientists conducted association studies based on a candidate gene approach. A candidate gene may have been selected for any number of reasons including biological plausibility for the phenotype of interest. In the late 1990s and early 2000s, many genetic association studies were conducted for both focal and generalized epilepsies; in fact, over 50 studies were conducted involving hundreds of genes (13,29). The general approach of these studies was to use common SNPs as genetic markers within a given candidate gene and compare the frequency of alleles in affected cases to those in unaffected controls.

These studies resulted in multiple conflicting and nonreplicable results, and ultimately failed to identify any definitive common genetic risk factors for epilepsy (13,30). One of the reasons for this inconsistency of results is the inability to accurately account for population stratification in these analyses.

### Genome-Wide Association Studies in Epilepsy

Candidate gene studies came up short not only in epilepsy but also in many other disorders, and scientists recognized that a genome-wide approach was needed to obtain unbiased assessment of markers throughout the genome. Two aspects of human population genetics indicated that an “indirect approach” of assaying a set of genetic markers – even if the markers themselves had unknown functional effects – would still capture most of the common patterns of variation in the human genome and thus detect regions of the genome associated with a phenotype (31). The first relevant human population genetics observation was that approximately 90% of the genetic variants among individuals are common variants (MAF>5%) (32). The second was that the majority of common variants arose from a single mutation event that occurred on an ancestral chromosome and thus these SNPs frequently occur in combination with nearby variants.

Around the same time, two critical large-scale efforts toward understanding variation in the human genome

made this vision realistic: the human genome project (draft announced in 2000) and the International HapMap project (first data release in 2003). In addition, microarray technology enabled high-throughput genotyping of hundreds of thousands of SNPs. This led to the advent of the GWA studies.

GWA studies use dense arrays of genetic markers, typically SNPs, to survey a large proportion of common variants in the human genome. SNPs are either genotyped directly or indirectly through linkage disequilibrium. Linkage disequilibrium (LD) is the nonrandom association between alleles at different loci; these loci are often in close physical proximity since the likelihood of recombination between two sites increases with the distance between them. GWA studies attempt to identify associations between genotype frequency and trait status (affected patient vs. healthy individual). The effect size describes the increased population risk for a given trait that is conferred by a given genetic variant. GWA studies have had some success in common diseases; however, the associated SNPs typically have modest effect sizes and even when all associated variants are considered collectively, they still explain only a small fraction of known heritability and thus have limited translational potential in the clinic. A current catalog of published GWA studies can be found at the National Human Genome Research Institute's (NHGRI) website (<https://www.genome.gov/26525384>).

To date, three GWA studies have been conducted in epilepsy. The first study examined focal epilepsy patients of European ancestry (33). This was a phenotypically heterogeneous cohort, in that all focal epilepsies, regardless of syndrome or possible structural-metabolic causes, were included. This resulted in a cohort of nearly 3,500 cases and about 7,000 controls with no history of seizures. It is now widely accepted that the threshold for genome-wide significance in association studies is  $5 \times 10^{-8}$  (29); when correcting for the 528,745 SNPs genotyped in this study, the threshold required to achieve significance was  $9.46 \times 10^{-8}$ . However, the top SNP in this study had a  $p$ -value of  $3.34 \times 10^{-7}$  and, thus, no SNPs were found to be significantly associated with the focal epilepsies (33). A second GWA study was also conducted in focal epilepsy patients; these patients were of Chinese ancestry (34). This GWA study was divided into two stages: a discovery stage (~500 cases (structural-metabolic focal) vs. ~3000 controls) and a replication stage (~600 cases (structural-metabolic or unknown focal) and ~500 controls). The initial discovery stage did not detect any variants of genome-wide significance. Next, they followed up a subset of SNPs with the lowest  $p$ -values (selected based on significance and regional LD structure) in the discovery stage by analyzing only these 80 SNPs in the replication stage and found one SNP that surpassed the threshold for genome-wide significance. This SNP resides on 1q32.1 in the *CAMSAP1L1* gene; this gene encodes a cytoskeletal protein whose biological connection to epilepsy is unclear. It is unclear if this finding is only relevant in this ethnic population, and external replication is needed to prove the

association with epilepsy. Finally, a third study was conducted in genetic generalized epilepsy (GGE) patients of European ancestry (35). Again, this GWA study was conducted in two stages: a discovery stage (~1500 GGE cases vs. ~2400 controls) and a replication stage with two independent cohorts (~600 parent-offspring trios, in which the unaffected parents were treated as controls, and an additional ~900 GGE cases and ~900 controls). No SNPs reached genome-wide significance in the discovery stage. For the replication stage, they selected a subset of SNPs with the lowest  $p$ -values in the discovery stage (selected based on significance and regional LD structure), resulting in the analysis of ~20 SNPs in the replication stage. Again, no SNPs reached genome-wide significance. Finally, they performed a combined analysis with stage 1 and stage 2 samples, and despite finding no associations of genome-wide significance, they highlight an SNP in the 5' untranslated region (5'-UTR) of *SCN1A*. *SCN1A* has the largest number of known epilepsy-associated mutations (36) and, thus, this low signal (rs11890028,  $P_{\text{meta}} = 4.0 \times 10^{-6}$ ) is likely due to this SNP being in LD with rare causal mutations in *SCN1A*. After separating the samples into two syndromic subgroups, genetic absence epilepsies (GAEs) and juvenile myoclonic epilepsy (JME), to look for syndrome-related variants, they also found weak non-genome-wide significant signals but larger samples sizes and replication will also be needed to prove these associations.

Taken all together, these three GWA studies provided only modest evidence for additional loci and replication of these signals is needed to prove their true association with epilepsy. This is likely due to a number of different factors. The first is simply that epilepsy is a highly heterogeneous disorder and thus obtaining large cohorts for well-powered association studies requires well-phenotyped and phenotypically homogeneous samples in very large numbers. Second, it is possible that the true causal variants exist at lower frequencies in the population and thus multiple rare causal variants of large effect may be driving the diluted signals observed when assaying common variants, and thus direct identification of the causal variants may provide a better approach (37).

## COPY NUMBER VARIATIONS

Deletions, insertions, duplications, and complex rearrangements of large segments of genomic DNA are all forms of structural variation (Figure 2.1). CNVs are submicroscopic structural variants. They are similar to SNPs, in that they occur throughout the human genome and confer inter-individual genetic variation. If a CNV is present in about 1% of the human population, it is called a copy number polymorphism (CNP). An SNP alters a single nucleotide pair, whereas a CNV alters anywhere from one thousand base pairs (one kilobase, Kb) to several million base pairs (megabases, Mb) of DNA. Recurrent CNVs are CNVs where the end points (beginning and end of a duplication or deletion) are limited to a narrow genomic region with extensive

homology. The homology of these regions makes it more likely for these CNV events to occur and, thus, these CNVs are found in multiple individuals. In contrast, nonrecurrent CNVs have very limited homology at their end points, and thus the same end points are rarely observed in the human population.

While there are many more SNPs than CNVs in the human genome, CNVs impact a larger proportion of the genome, with at least 10% of the genome being subject to CNV (38). CNVs are found in both gene-rich and gene-poor regions. CNVs are a major genetic component of phenotypic diversity; they can be nonpathogenic and are observed in “healthy” individuals with no clinical diagnosis.

### The Role of Copy Number Variants in Epilepsy

The failure of association studies to discover common variants with a clear effect in epilepsy suggested that rare variants (found in <1% of the population) might be underlying the etiology of epilepsy. Further support of this hypothesis came from a number of studies in other neurological disorders, where strong evidence emerged for rare CNVs conferring increased risk for intellectual disability (39) and schizophrenia (20). In addition, the study of rare CNVs revealed that a single CNV might be associated with a wide range of clinical phenotypes. For example, in 2008, a recurrent microdeletion at 15q13.3 was separately associated with schizophrenia (20,40), autism, and other neuropsychiatric features (41), as well as epilepsy and mental retardation (19). In 2009, this recurrent 15q13.3 microdeletion was tested in a cohort of common epilepsy patients, and found to confer increased risk for GGEs (17). This “critical region,” or minimum deleted region across all observed patients is 1.5 Mb. This 1.5 Mb region contains seven genes, including a plausible epilepsy candidate gene – *CHRNA7* that encodes a subunit of the nicotinic acetylcholine receptor. Two additional recurrent CNVs at 15q11.2 (42) and 16p13.11 (16,42) have also been associated with the common epilepsies. The microdeletion at 16p13.11 is found in GGE and partial epilepsy patients (16).

In summary, there are three recurrent CNVs that increase epilepsy risk: 15q11.2, 15q13.3, and 16p13.11. These microdeletions are especially important for the GGEs and they are also shared risk factors for other neuropsychiatric disorders, such as, schizophrenia, autism, and intellectual disability. Collectively, these three CNVs account for an estimated 2.9% of patients with genetic (a.k.a. idiopathic) epilepsies (2).

Nonrecurrent CNVs are also potential risk factors for all types of epilepsy. No single nonrecurrent CNV will account for a large proportion of epilepsy patients; however, these CNVs may include known epilepsy genes or may highlight novel candidate genes (CNVs with different end points may have a “critical region” that impacts the same novel gene). For example, in a study of ~500 epilepsy patients, two patients harbored microdeletions involving *AUTS2*

(previously associated with autism) and one harbored a microdeletion involving *CNTNAP2* (previously associated with autism, Cortical dysplasia-focal epilepsy syndrome, and Pitt-Hopkins like syndrome 1). These are relevant to epilepsy, given the association of these genes with other neurodevelopmental and neuropsychiatric disorders (2). Investigations of CNVs in epileptic encephalopathy found that nearly 4% of patients harbor rare and clearly pathogenic CNVs (43). More generally, large heterozygous deletions (>1 Mb) are significantly enriched in epilepsy patients, and completely absent from controls when larger than 2 Mb in size (16). Proving the causality of these rare or singleton CNVs will be difficult and will likely require very large sample sizes and/or independent evidence for the candidate gene (eg, association of non-CNV mutation).

Currently, the most well-established epilepsy associated CNVs are all deletions; however, this does not to exclude the possibility that pathogenic duplications also exist.

### The Mechanism of Copy Number Variant Pathogenicity

It is clear that phenotypic heterogeneity is associated with risk CNVs and it is also clear that some CNVs are not completely penetrant. The mechanism of pathogenicity for CNVs is not clear and may vary depending on the locus itself (location in the genome) or the individual genome of the patient. In many cases, a phenotype may be attributable to a single gene within the CNV; for example, a microdeletion of *SCN1A* in a Dravet syndrome patient. For other microdeletions, the phenotype may be simply due to haploinsufficiency (only one copy of the gene does not result in enough of the gene product) of all the genes within the CNV. Alternatively, there may be a deleterious variant present in a gene on the nondeleted homologous chromosome leaving no wild type copies of the gene. Regardless of the mechanism, rare copy number variants play an important role in epilepsy susceptibility.

### LARGE STRUCTURAL VARIANTS

Large structural variants (>3 Mb) can be detected by cytogenetics, which is microscopic analysis of chromosomes in individual cells. There are three main cytogenetic analyses performed in the clinical laboratory: G-banding karyotypes, fluorescence in situ hybridization (FISH), and chromosomal microarrays. Chromosomal microarrays provide the highest resolution of the three techniques and can detect submicroscopic abnormalities that are too small to be detected by conventional karyotyping (ie, CNVs).

These cytogenetically detectable variants are less frequent in the human genome than CNVs and are often pathogenic. Cytogenetic analysis is particularly helpful for epilepsies occurring with mental retardation or dysmorphic features. Eight syndromes involving seizures are caused by a recurrent chromosomal abnormality; these are referred to



as the “chromosomal epilepsies” and include Down syndrome, Angelman syndrome, Miller–Dieker syndrome, Wolf–Hirschhorn syndrome (4p deletion), Chromosome 1p36 deletion syndrome, 15q inversion-duplication, Ring chromosome 14, and Ring chromosome 20 (44). In addition, Fragile X patients also frequently experience seizures. This disorder is often discussed among the chromosomal epilepsies because early research revealed that these patients frequently had a detectable fragile site on the X chromosome, at which the chromosome was prone to breakage. We now know that this disorder is caused by mutations in the *FMR1* gene, most commonly an expanded CGG triplet repeat mutation. Thus, despite a commonly detectable abnormality in the X chromosome, fragile X is actually classified as a trinucleotide repeat disorder.

## NEXT-GENERATION SEQUENCING STUDIES

The Human Genome Project sought to sequence the entire human genome, in other words, to determine the exact order of the base pairs in the human genome. This project used DNA from multiple anonymous volunteers and took over ten years to complete. Next-generation sequencing (NGS), also known as massively parallel sequencing (MPS), has revolutionized the cost and speed with which a human genome can be sequenced – with genomes now being sequenced within a week. While the technical details vary by the sequencing platform used, these high-throughput sequencing approaches generate millions of short sequence reads in parallel. These short sequence reads can then be aligned to the human reference genome (generated by the Human Genome Project). A computer algorithm is then used to perform “variant calling,” which results in the identification of all alleles in the newly sequenced genome that differs from the reference genome, including SNVs and indels. Additional algorithms have also been developed to identify structural variants from whole genome and exome sequence data (45–47). In exome sequencing, an additional step is included prior to sequencing, which targets and captures only the exonic and flanking intronic base pairs. Exome sequencing is popular for two main reasons: (a) a majority of known disease-causing mutations are in protein coding regions of the genome and (b) exome sequencing targets about 2% of the human genome and thus is cheaper and faster than whole genome sequencing. In contrast, whole-genome sequence data can be used to identify noncoding variants whose function we will likely understand more fully in the coming years with the advent of projects like the ENCyclopedia Of DNA Elements (ENCODE) (48).

### Next-Generation Sequencing Study Designs

NGS facilitates a thorough analysis of nearly all genetic variants in the genome, including very rare variants not directly analyzed using GWA methods. These genetic variants must be prioritized differently for different diseases and study

designs. At the broadest level, a number of factors should be considered, including the mode of inheritance (eg, if recessive, then focus on homozygous variants), the frequency of the disorder (eg, if the disorder is rare, the causal variant(s) will be very rare or absent in controls), and predicted deleterious nature of the variant itself. Finally, a variant-based approach could be used if the hypothesis is that causal variants will have a relative large effect and will be present in multiple cases. In contrast, if the causal variants are individually very rare in the case population but are hypothesized to lie within the same gene(s), then gene-based approaches should be used.

Research has already established that in Mendelian disease, whole genome or exome sequencing of even just a small number of cases can readily identify the causal variants as those that are shared among a small number of unrelated affected individuals and rare in the general population (49–51). In contrast, a number of different NGS study designs can be considered for optimizing discovery of disease-associated variants for complex diseases. First, a classical case–control study design can be used in which a large number of case samples and ethnically matched controls are sequenced to detect variants (or genes with qualifying variants) that are enriched in the case population. The main disadvantage to this approach is that very large sample sizes are needed, which is still cost prohibitive, to perform sufficiently powered whole-genome association studies. However, power can be increased by either restricting the tested variants based on a priori predictions of the functional impact of the variants or by sequencing individuals on one or both extreme ends of a phenotypic distribution (52).

Second, a trio-based design can be used in which the healthy biological parents and affected children are sequenced and newly formed genotypes (eg, de novo, newly homozygous) are identified in the child. The human mutation rate is between  $1 \times 10^{-8}$  and  $2 \times 10^{-8}$  per base pair per generation, which equates to roughly 40 de novo mutations per generation. Therefore, each individual is expected to have only about one exonic de novo mutation. De novo mutations, particularly those predicted to damage an encoded protein, can be disease causing and are increasingly surveyable with NGS trio studies.

Third, if families with multiple relatives affected with a complex disease exist, then family-based studies can be utilized. While any number of relatives could be selected for sequencing, one cost-effective strategy would be to sequence distantly related diseased individuals to minimize the number of variants shared by chance while still enriching for any shared risk variant(s). These shared variants can then be tested for cosegregation of the variant with affectation status in the entire family pedigree.

To date, a number of different NGS studies have been conducted with the goal of uncovering new risk factors for epilepsy and epilepsy-related syndromes. These are described further in the following paragraphs.

### Case–Control Study in Genetic Generalized Epilepsy

A case–control study of 118 GGE (previously known as idiopathic generalized epilepsy) cases and 242 controls of European ancestry were exome-sequenced to evaluate the role of rare variants of relatively large effect that are frequent enough to be present in multiple cases (53). Specifically, this cohort of 118 GGE cases included 93 juvenile myoclonic epilepsy patients and 25 absence epilepsy patients. Despite restricting the tested variants to SNVs with an  $MAF < 5\%$  that were predicted to disrupt the protein-coding sequence, this exome-sequencing–based association testing failed to identify any variants that were significantly associated with GGE. In addition, a second stage of this study went on to genotype a subset of the SNVs identified by exome-sequencing ( $n = 3,897$ ) in a larger case–control cohort of 878 GGE cases and 1,830 controls also failed to identify variants significantly associated with GGE. This work highlights the extreme genetic heterogeneity of epilepsy disorders and also suggested that gene-based analyses (as opposed to variant-based) and/or more homogeneous phenotypic cohorts are needed to reveal true risk factors for the GGEs.

### Other NGS Studies in Epilepsy

There have been a handful of other NGS studies in epilepsy; primarily these have investigated specific epilepsy syndromes with familial inheritance patterns.

For example, multiple families with autosomal dominant familial focal epilepsy with variable foci (FFEVF) had previously shown linkage to 22q12, but the causal gene had yet to be identified. Therefore, two different research laboratories took the same approach; they (a) selected families with linkage to this region, (b) performed exome-sequencing on one or more family members, (c) identified rare protein-coding variants in this linkage region, and (d) tested these variants for cosegregation in the whole family. This resulted in the identification of causal mutations in *DEPC5* (24,25).

Another example is benign familial infantile epilepsy (BFIE) is an autosomal dominant seizure disorder where many families showed linkage to 16p11.2–16q12.1, but the causal genetic mutations evaded discovery for many years. Therefore, one research group designed a targeted capture for genes in this linkage peak, ultimately resulting in the identification of *PRRT2* as the causal gene (26). However, this discovery was in fact only due to Sanger sequencing of the *PRRT2* gene because the coverage (number of short sequencing reads at a given site) was too low to accurately call variants in this gene (26). This highlights one of the technical pitfalls of NGS: coverage must be relatively high (typically  $>30\times$  on average across the genome) to accurately detect variants, and this can be difficult in certain regions of the genome (eg, GC-rich).

### De Novo Mutations in Epileptic Encephalopathies

The critical contribution of de novo mutations to neurodevelopmental disease risk has recently been elucidated (54–56). To investigate the role of de novo mutations in epileptic encephalopathies, a large collaboration was established between the Epilepsy Phenome/Genome Project (EPGP) and the Epi4K Consortium (57). This research focused on two main types of epileptic encephalopathies, infantile spasms (IS) and Lennox–Gastaut syndrome (LGS). Exome sequencing was performed on a total of 264 probands and their unaffected biological parents (58). All putative de novo mutations were identified and subsequently validated by Sanger sequencing, resulting in an average of 1.25 de novo mutations per trio. This work identified two new epileptic encephalopathy genes and provided suggestive evidence for the role of several other genes. The two new genes both have clear statistical evidence of association with epileptic encephalopathy with four patients harboring different *GABRB3* de novo mutations and two patients with the same de novo mutation in *ALG13*.

A number of studies have also used targeted capture to sequence only a subset of relevant genes. One such study sequenced nine known and 46 candidate genes for epileptic encephalopathy in 500 cases (27), resulting in the association of epileptic encephalopathy with de novo mutations in two novel genes: Chromodomain Helicase DNA Binding Protein 2 (*CHD2*) and Synaptic Ras GTPase Activating Protein 1 (*SYNGAP1*) (27). A second study sequenced 35 known or potential candidate genes in 53 epileptic encephalopathy patients (59), resulting in the identification of a number of causal de novo mutations in previously known genes.

### De Novo Mutations in Epilepsy

When looking at epilepsy more generally, there has still been a strong focus in the community on the identification of de novo mutations. This has resulted in an increasing number of candidate genes. In fact, in a Pubmed search (June 20, 2013) for the term “De novo mutations + seizure” returned 244 primary papers highlighting a gene or structural variant linked to clinical manifestations of seizure. Within these papers, 65 unique genes have been identified, as well as 91 structural variants. Several genes were reported in multiple papers, including *SCN1A* (35), *CDKL5* (11), *PCDH19* (9), and *KCNQ2* (7). Further classification of these genes revealed that 11 are known epilepsy genes (12), 11 are associated with epilepsy in the Human Gene Mutation Database (HGMD, <http://www.hgmd.cf.ac.uk/ac/index.php>), 16 are included on an epilepsy NGS gene panel (28), eight are listed with an association to a known “condition with seizures” on Genetics Home Reference (<http://ghr.nlm.nih.gov>), two genes harbor de novo mutations in patients with Autism Spectrum Disorder (55,56,60,61), one is a mouse seizure susceptibility gene (62), four are known ion channel genes (63), and 12 do not fall into any of these categories.

While many of these de novo mutations are likely disease causing, each de novo mutation should be considered on a case-by-case basis. In general, a coding mutation that is predicted to be deleterious in a previously established gene is considered causal. For newly implicated genes, additional observations of mutations in other phenotypically similar patients are necessary in order to prove causality; a good framework for such analyses has recently been established (58). As sequencing continues to drop in cost and as sample sizes grow, the discovery of additional de novo mutations will help to widen our understanding of the genetic basis of epilepsy and other related seizure conditions.

## PHARMACOGENOMICS

Genetic variation can not only confer disease risk or protection but may also influence how a patient responds to medications. The study of the role of genetics in pharmacologic response, or pharmacogenetics, is particularly relevant in epilepsy disorders, since nearly all epilepsy patients undergo drug therapy for some period of time, and an estimated 30% of patients become drug resistant and never achieve seizure freedom despite treatment with all available antiepileptic medications.

Several genetically based hypotheses exist for why some patients fail medications that can control seizures in other patients with the same diagnosis. One hypothesis, the pharmacokinetic hypothesis, is that genetic variation causes differences in the absorption, metabolism, or distribution of antiepileptic drugs in the brain (64). In this model, a drug-responsive patient receiving a medication will get adequate concentrations of medication to the brain, whereas a drug-resistant patient will be unable to achieve sufficient medication levels in the brain to achieve seizure control. To date, the only consistently replicated evidence supporting this hypothesis is the association of variants in genes encoding a drug-metabolizing enzyme, CYP2C9, with phenytoin (a common antiepileptic drug) metabolism (65–67). Given the relatively minor consequences of the variation on the antiseizure response of phenytoin, the clinical utility of using CYP2C9 genotype to predict phenytoin dosage requirements is unclear. Despite this uncertain clinical relevance, dosing adjustments have been published recommending a 25% reduction in maintenance dose for the CYP2C9 \*1/\*2 and \*1/\*3 genotypes; a 50% reduction in maintenance dose for the CYP2C9 \*2/\*2, \*2/\*3, and \*3/\*3 genotypes; and cautious monitoring for adverse drug reactions associated with phenytoin toxicity (sedation, ataxia, nystagmus, dysarthria) (68). An alternative hypothesis is the pharmacodynamic hypothesis, where the gene encoding a drug target is mutated, and this change prevents the medication from being able to effectively modulate the intended pathway (69). There are no consistent reports of mutations in genes encoding drug targets or their modulators associating with response to antiepileptic dosing. It should be noted, however, that pharmacogenetic studies of antiepileptic medications performed to date

have primarily evaluated the role of common variants (MAF >5% in the population) and are often statistically underpowered to robustly detect genetic associations. Larger studies considering less common variation are needed to better explore the aforementioned hypotheses.

In addition to there being little evidence to support either the pharmacokinetic or pharmacodynamic genetic hypotheses, they also fail to explain why a large number of drug-resistant patients fail to respond to multiple medications that are substrates for many different transporters at the blood–brain barrier and have differing modes of pharmacologic action. That is, under both of these hypotheses, many universally drug-resistant patients would have to have multiple mutations in genes encoding drug transporters governing drug disruption, metabolic pathways mediating metabolism, and/or pharmacologic targets. While it is possible that some patients may have acquired diffuse nongenetic changes due to seizures that are responsible for multidrug resistance, some patients present at the onset with drug-resistant seizures, and, despite aggressive early interventions, fail to respond. Recently, it has been proposed that drug-resistant epilepsy may reflect an intrinsically more severe form and that seizure control is therefore more difficult from the onset (70). One interesting additional possibility stemming from this hypothesis is that certain forms of epilepsy are not necessarily intrinsically more severe, but rather they arise from pathophysiologic changes that are not correctable with current pharmacologic agents. Therefore, what appears to be more severe epilepsy may in fact be a specific subtype of epilepsy with a currently unknown biologic etiology. Additional research is needed to reveal the neurobiological and genetic aspects of drug resistance, particularly as it pertains to the interplay of drug resistance and underlying pathophysiology.

Genetic variation can also dictate if a patient will experience severe adverse drug reaction to a medication. For antiepileptics, two clear genetic associations of HLA (human leukocyte antigen) alleles with cutaneous hypersensitivity reactions have been identified. First, in 2004, Chung *et al.* first reported a strong association between the presence of the HLA-B\*15:02 allele and carbamazepine-induced Stevens-Johnson syndrome, a severe hypersensitivity reaction, in patients of Han Chinese descent. In this study, the HLA-B\*1502 allele was present in 100% (44/44) of patients with carbamazepine-induced Stevens-Johnson syndrome, while only 3% (3/101) of patients on carbamazepine with the HLA-B\*1502 allele had no reaction (71), indicating that the presence of this allele is highly predictive of this severe reaction to carbamazepine. These results were later replicated in the Han Chinese population and in other Asian populations, and were expanded to include toxic epidermal necrolysis, another severe cutaneous hypersensitivity reaction (72). Based on these findings and the frequency of the HLA-B\*1502 alleles in Asian populations, the Food and Drug Administration currently recommends that all high-risk populations, including individuals of Han Chinese

descent, and individuals from Vietnam, Cambodia, the Reunion Islands, Thailand, India, Malaysia, and Hong Kong, be screened for the presence of the HLA-B\*1502 allele prior to initiating carbamazepine drug therapy. Limited evidence suggests that the HLA-B\*1502 allele may also increase the risk of phenytoin-induced severe hypersensitivity reactions (73), which has led to the inclusion of a statement of caution in the drug label for phenytoin.

In addition to the risk of hypersensitivity reactions associated with the HLA-B\*1502 allele, two recent GWA studies in patients of European and Japanese ancestry showed an association of an allele of the gene encoding the human leukocyte antigen A (HLA-A\*3101) was associated with a range of carbamazepine-induced hypersensitivity reactions, including maculopapular exanthema, hypersensitivity syndrome, and the more severe Stevens-Johnson syndrome and toxic epidermal necrolysis (74,75). This association was not as strong as that seen for HLA-B\*1502, with only moderately increased risk for hypersensitivity reactions (74,75). Unlike HLA-B\*1502, HLA-A\*3101 does not increase the risk of hypersensitivity to other aromatic antiepileptic medications, including lamotrigine and phenytoin (76). There are no current recommendations on genotyping HLA-A prior to carbamazepine treatment.

## CLINICAL GENETIC TESTING

There are several varieties of genetic testing, including biochemical assays, cytogenetics, Sanger sequencing (typically used for single gene testing), and NGS (used for gene panel sequencing or whole-exome sequencing). Genetic testing can determine a genetic diagnosis, which, in turn, helps guide patient care and counseling about prognosis and reproductive choices for the parents. In addition to diagnostic testing, predictive testing may be valuable for patients with a family history of epilepsy. In the United States, all genetic testing that will be used for medical management or intervention for a patient must be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Access to a genetic counselor should be provided to help the patient and their family understand the results and their implications.

It is critical to be aware of the current speed of genetic discovery because this dictates the growth in the field of genetic testing, with new information emerging practically every day. In epilepsy genetic testing, there are guidelines established for the clinical utility of testing the most commonly mutated genes (12,44). For example, screening of *SCN1A* in Dravet syndrome or *CDKL5* in infantile spasms are useful screens because mutations (typically de novo) explain 70% to 80% and 10% to 17% of cases, respectively (11). In patients experiencing seizures with cortical malformation, one of the most common diagnoses is periventricular nodular heterotopia (PNH). The most common cause of familial PNH and nearly 25% of the nonfamilial forms are caused by mutations in the *FLNA* gene; again making this a logical first diagnostic screen (43). For a small proportion of genes, knowing the genetic etiology can guide treatment, as

is the case for *SLC2A1* mutation-positive patients (“GLUT1 deficiency syndrome”) where the ketogenic diet is the gold standard of treatment (77).

Chromosomal microarray analysis and karyotyping should be used to detect structural abnormalities; this is particularly critical for patients with seizures who exhibit mild or moderate intellectual disability and/or dysmorphic features. In this case, fragile X testing and biochemical testing of amino acid levels may also be useful (43). CNV screening appears to be critical in two main groups: epileptic encephalopathy (CNVs explain ~4% of cases) (43) and GGE with intellectual disability (CNVs explain ~10% of cases) (78).

In patients where the first genetic screen is less obvious, or if screening of multiple genes has failed to identify the disease-causing variant, ordering a comprehensive panel of genes is a very practical approach. For many diseases, including epilepsy, gene panels are offered for genetic testing; gene panels target a set of genes that are associated with a given disorder. Sequencing of these genes is usually achieved by NGS of the coding exons and the flanking intronic boundaries. The set of genes included may vary by the company performing the CLIA-certified sequencing. For example, GeneDx offers a number of different epilepsy gene panels. The most comprehensive panel includes 71 genes, but smaller panels are available that target infantile or childhood-onset seizures. The Courtagen epiSEEK gene panel includes over 300 genes. Current lists of all available genetic tests and testing facilities are available online and updated regularly (<http://www.genetests.org> and <http://www.orpha.net>).

From a clinical perspective, it is practical to order a phenotypically relevant gene panel than to order exome sequencing. One reason for this is that variants identified in genes selected for a gene panel will be more interpretable based on prior knowledge; in contrast, opening interpretation up to the exome may generate a long list of variants of “unknown clinical significance.” In addition, this avoids issues associated with “incidental genetic findings,” which may arise when interrogating the exome. However, if the patient has a very unique phenotype, exome-sequencing may be a more desirable approach than a gene panel. Finally, it is usually helpful to also have parental DNA available for testing to determine the inheritance (ie, de novo status) and thus likely pathogenicity of any identified variants.

The scientific community has made important strides toward understanding the genetic etiology of the epilepsies. While, there is still a long way to go, let us first summarize what we now know. First, only a few rare types of epilepsy are caused by mutations in single genes where these mutations segregate in families according to Mendel’s laws. The majority of genes in this category have likely been identified already, at least if these families have been ascertained already. Any remaining cases of “low hanging fruit,” such as families with linkage peaks (like *DEPC5* [24,25]), will likely be solved in the near



future with NGS. Collectively, mutations in these genes explain an estimated 1% of epilepsy cases. Second, the findings from these families have informed the biology of epileptogenesis and shown that diverse classes of genes can lead to sporadic epilepsy and syndromic forms of epilepsy. The genotype–phenotype correlations observed in these genes also prove the locus heterogeneity and variable expressivity that confound traditional genetic approaches. Third, despite the lack of clear associations between common variants and epilepsies, they have informed our understanding of the genetic architecture and focused our efforts toward rare variants. Fourth, CNVs also confer increased risk for epilepsy. Although the mechanism of pathogenicity is not clear for many of these CNVs. Fifth, large-scale exome-sequencing of GGE cases failed to identify any variants of large effect. This suggests association tests at the gene level are more promising and also highlights the high genetic heterogeneity that likely exists in complex epilepsies. While trio-based NGS studies have been particularly successful in the epileptic encephalopathies, we are still only explaining an estimated approximately 12% of *SCN1A* mutation–negative patients. Based on the large-scale sequencing efforts in IS and LGS, it has been estimated that nearly 90 genes confer risk (58), again highlighting the extreme genetic heterogeneity for the epilepsies.

So where do we go from here? How can we identify additional risk factors for the epilepsies? In the complex epilepsies, it seems possible that hundreds of different genes are responsible and each would explain only a very small proportion of epilepsy cases. Without massive sample sizes, obtaining sufficient evidence for genes of small effect will be nearly impossible. In addition, the complex inheritance patterns also suggest that gene–gene or gene–environment interactions may play a role in epilepsy risk. Obtaining sufficiently powered cohorts to examine these questions is extremely challenging. For example, consider if the gene–gene interaction is a “two-hit” model, given the low frequency of risk alleles and the extreme genetic heterogeneity of epilepsy, it would be very difficult to identify even the “first hit” in enough samples to search for the second hit in a sufficiently large cohort to correct for testing interactions between loci. There is one ongoing large-scale effort to perform NGS sequencing of ~300 multiplex families (>3 affected individuals, many with non-Mendelian inheritance patterns) and another 1,500 pairs of first-degree relatives with epilepsy (57). This work will likely reveal additional risk factors for the epilepsies.

Finally, nonprotein coding mutations have yet to be directly and thoroughly investigated for their association with epilepsy. It is conceivable that noncoding mutations lie in regulatory regions altering gene expression of known or novel epilepsy genes. Alterations to the epigenome—chemical modifications to the DNA and histones, which alter the overall genome structure, tightly compacting inactive genes—may also impact gene expression and

lead to disease. Epigenetic marks differ by cell type and are dynamic throughout life, responding to environmental changes, and thus studying epigenetics demands directly studying the tissue of interest. Another hypothesis is that somatic mutations, occurring in critical brain regions, explain some proportion of epilepsy cases. Testing this hypothesis would also require access to brain tissue. Finally, recent evidence has emerged supporting a possible role for a class of small (~22 nucleotides), noncoding RNA called microRNA (miRNA) in epilepsy. MiRNA molecules posttranscriptionally regulate the level of mRNA for a gene and miRNAs can target multiple genes/proteins.

One central question is how will we go from identification of epilepsy genes to targeted therapies for patients with mutations in these genes. As exemplified by cystic fibrosis, this process can take an extremely long time. The *CFTR* gene was identified in 1985 and the first drug specifically acting on *CFTR* was available over 20 years later (79). One important step in drug development is showing efficacy in animal models. Epilepsy has been studied in rodents for many years. The physiological end point for epilepsy, a seizure, is readily detectable in rodent models. A large number of genes are associated with seizures in mice, including both human epilepsy genes (Table 2.2) and novel genes not yet associated with human phenotypes (62). Interestingly, gene knock-outs on different genetic backgrounds (mouse strains) show variation in seizure penetrance, suggesting these mice may also be good models for complex epilepsies. In drug development, mouse models are a very powerful tool; however, they can also be a rate-limiting step. One alternative is to model human mutations in cellular systems. It is now possible to rapidly and cost-effectively “edit” cells to introduce the mutation(s) of interest using RNA-guided DNA endonuclease (CRISPR) approaches (80). Appropriate disease-modeling requires assaying relevant cell types; therefore, it is also critical that recent developments in induced pluripotent stem cell (iPSC) technologies enable differentiation into a range of cellular populations. For epilepsy modeling, these two technologies can be combined, resulting in CRISPR editing of iPSCs and subsequent differentiation into different types of neurons. Then the electrophysiology and overall network behavior can be examined in these living neuronal networks by multi-electrode arrays (MEAs). To screen drugs in a mutation-dependent fashion, MEAs can be used to first assess the mutant neuronal phenotypes (compared to wild-type neuronal networks) and then treat the cells with drugs/compounds to screen for those that restore wild-type phenotypes. In addition, phenotypic comparisons among mutations in different genes can also be used to assemble epilepsy mutations into distinct functional groups, which may respond similarly to the same drug compounds. Such an approach offers a medium-throughput method for screening drugs in a genetically informed way and will facilitate the identification of new epilepsy drugs.

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# Epileptic Seizures

Matthew W. Luedke and Rodney A. Radtke

## 3

C H A P T E R

Recent advances in epilepsy and neurophysiology have naturally made the field more complex. As video electroencephalography (vEEG), continuous EEG (cEEG), and invasive EEG monitoring have developed, so too has our understanding of seizure semiology, localization, and evolution of disease (1). Revolutions in genetics, biochemistry, and functional neuroanatomy have deepened our understanding of pathophysiology, replacing descriptive distinctions among seizures and syndromes with actual etiologies and mechanism (1,2). Epileptologists have struggled to express this growing complexity with clinically and scientifically useful language.

The informal 19th- and early 20th-century categories of *grand mal*, *petite mal*, and psychomotor seizures were clinically expedient, but limited in detail. Moreover, contemporaries worried that the terms *grand* and *petite* unintentionally connoted severity, and that the tripartite categories implied a lack of overlap (3).

In the second half of the 20th century, there was a movement toward an internationally accepted nomenclature, intended to facilitate communication in clinical and research settings. The International League Against Epilepsy (ILAE) played an early role, beginning in the 1960s. In 1970, the ILAE proposed a formal classification for seizures and epilepsy, with standardized clinical and EEG criteria (4).

These original classifications were updated in 1981, but the revisions preserved the foundational language and electroclinical definitions (5). The ILAE drastically revised its terminology in 2010, opting for a more semiologic nomenclature for seizures (6). Current clinical practice tends to hybridize the two systems, and there is ongoing debate as to the practicality and validity of both systems.

This chapter will describe the two dominant schemes for seizure classification: the 1981 ILAE nomenclature for seizures and the recent 2010 ILAE guidelines. Cases will be provided to illustrate and compare the two systems in a clinical setting.

## CONSIDERATIONS IN CLASSIFICATION

Classification schemes lie at the intersections of math, philosophy, and science, and can be conceptually complex; but, for the purposes of this chapter, classification will be accepted as the systematic grouping of phenomena, based off of real and meaningful differences among groups (2,7–9). Seizures represent a challenge for systematic organization. Clinically, seizures are protean, with manifestations ranging from subjective sensations to altered consciousness to convulsions. Not only are the component manifestations important, but also their sequence is critical to localization. Thus, semiology is an obvious target for classification (10).

Seizures are also described electrographically, and with the expansion of vEEG and intracranial monitoring, there are abundant electroclinical data available to characterize seizures. Electrographic characterization, like semiology, is a tempting target for seizure classification, particularly for seizures with classical electrographic morphology, like absence.

Recently, the ability to describe at least some seizure subtypes using the language of cellular and molecular biology and neural networks has helped with classification. Absence seizures, for example, are thought to be generated by abnormal T-type calcium channel function and self-sustaining derangements in thalamo-cortical circuits (11). Ostensibly, as the understanding of neuroscience expands, more subtypes of seizures will have identifiable causes at the cellular and biochemical levels, providing yet more options for categorization.

Criteria aside, the intention of a classification system is also critical. When it comes to describing seizures, clinicians have a bias toward pragmatism and generalizability. Researchers tend toward granularity and precision. The ideal would be a system that is not only user-friendly at the bedside, but also communicates detail about pathophysiology at bench (7). Such a happy medium is elusive, and has been an ongoing challenge in seizure classification.



## THE 1981 RECOMMENDATIONS FOR THE CLASSIFICATION OF SEIZURES

The first attempts to classify seizures in the 1960s to 1980s brought uniformity to the language of epileptologists (4,5). This was an era of early development in seizure monitoring. Video with synchronized EEG data was newly available. Thus empowered, the committees developed an electroclinical language, based partly on the enthusiastic presumption that EEG and semiology had a direct relationship.

The first proposed ILAE classification of seizures was published in 1970, two years before the public announcement of the EMI scanner (12). These guidelines accepted that seizures arose from either a focal region, or more broadly across both hemispheres of the brain. As computed tomographic (CT) imaging evolved through the 1970s, this, too, informed the structural basis for the 1981 revision of the nomenclature. As more vEEG became available and as better functional and anatomical imaging evolved, some of the inaccurate assumptions of the 1970 recommendations became apparent. Between 1970 and 1980, several working groups vetted the guidelines and produced a revision in 1981. The revision preserved the core language of the 1970 recommendations and refined the electroclinical system. The criteria are summarized herein, and in Table 3.1 (5).

## Partial Seizures

A seizure is partial when the initial clinical and electrographic manifestations indicate an origin in one cerebral hemisphere. Onset is the critical component, as a partial seizure can subsequently generalize to both hemispheres. This marks the first major division of partial seizures: partial seizures evolving to secondarily generalized seizures, or partial seizures without generalization.

Regardless of evolution, partial seizures are then classified as simple or complex, with the adjective complex indicating an alteration in consciousness. Specifically, complexity requires a deficit in awareness of or response to the environment. It is further emphasized that this is not an issue of mental clarity or vigilance, but of a deficit in integrative processing, in order to exclude confusional states. As described, simple versus complex is a sharp dichotomy, though some clinicians, in practice, treat complexity as a spectrum of altered mentation.

### Simple Partial Seizures

Simple partial seizures are then described semiologically, noting their signs, symptoms, and their order of onset. Partial seizures can manifest with motor signs, somatosensory

**TABLE 3.1 Summary of the 1981 Recommendations for Clinical and Electroencephalographic Classification of Epileptic Seizures**

Simple Partial Seizures	With motor signs	
	With somatosensory or special sensory symptoms	
	With autonomic symptoms	
	With psychic symptoms	
Complex Partial Seizures	Simple partial onset	
	Impairment of consciousness at onset	
Partial-Onset Seizures Evolving to Secondarily Generalized seizures	Simple partial seizures evolving to generalized seizures	
	Complex partial seizures evolving to generalized seizures	
	Simple partial seizures evolving to complex partial seizures evolving to generalized seizures	
Generalized Seizures	Absence	Impairment of consciousness only
		With mild clonic components
		With mild atonic components
		With tonic components automatism
		With automatisms
		With autonomic components
	Atypical Absence	
	Myoclonic	
	Tonic	
	Clonic	
	Atonic (astatic)	
	Tonic–Clonic	
Unknown		

Source: From Ref. (5). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22(22):489–501.

or special-sensory symptoms, autonomic symptoms or signs, or with psychic symptoms.

Motor signs are manifold and can involve any part of the body. They can be elementary (those that can be recreated by electrically stimulating a muscle or a muscle group), tonic, dystonic, rhythmic, or a combination thereof. Motor activity can spread along contiguous muscle groups subserved by the motor homunculus—the “Jacksonian march”—or they can remain in a single muscle group. If these focal motor seizures are unremitting, they can be called *epilepsia partialis continua* (EPC). They can also resolve into paralysis (Todd’s paralysis).

Somatosensory or special sensory symptoms vary depending on the region of cortical involvement and are generally positive phenomena. Primary somatosensory seizures are felt as tingling (classically described as “pins and needles”), though proprioceptive distortions can occur. As with the Jacksonian march, there can be a contiguous spread of sensation along regions subserved by the sensory homunculus. Auditory and visual seizures are variable and depend on the proportion of primary sensory and association cortex involved. They can be elementary (tinnitus or scintillations, respectively) or complex (music, formed visual hallucinations). Olfactory seizures classically tend toward unpleasant odors. Vertiginous seizures are also categorized as special sensory events, and can mimic central vertigo or generate feelings of disequilibrium.

Autonomic seizures can manifest with both general autonomic or enteric phenomenon. Tachycardia, bradycardia, flushing, piloerection, pupillary dilatation, and diaphoresis are common general autonomic manifestations. Enteric phenomenon can include emesis, borborygmi, flatus, and bowel incontinence.

Psychic epileptic symptoms have a broad range of manifestations. Dysphasia can occur with preserved consciousness, and is seen in some simple partial seizures, as are distortions of memory and recall (*déjà vu*, *jamais vu*). The guidelines subtly acknowledge “cognitive disturbances,” such as feelings of detachment, unreality, or dream states, which may preserve integrative function enough that consciousness is not impaired. Similarly, isolated affective symptoms (eg, fear), illusions (eg, macropsia), and frank hallucinations may be a manifestation of a simple partial seizure.

EEG findings defined for simple partial seizures, both ictal and interictal, are local discharges over the region of cortex subserving the clinical signs and symptoms. Of note, the guidelines acknowledge that scalp recordings often do not capture electrographic changes in simple partial seizures, making their semiology critical for their identification.

### ***Complex Partial Seizures***

Complex partial seizures can evolve either from simple partial seizures, or they can begin with altered mentation *de novo*. If it originates as a simple partial seizure, somatosensory, special sensory, autonomic, and psychic symptoms

present prior to the onset of dyscognition are considered an aura. However, it can be difficult to judge the presence of preceding experiential symptoms because of periictal amnesia in many complex partial seizures. When originating with simple motor components, complex partial seizures can readily be described by the evolving motor phenomena.

Complex partial seizures can be further dichotomized into seizures with and without automatisms. Automatisms are complex release behaviors that emerge with the impairment of consciousness. They are learned behaviors, though they may be out of context or dyspractic, and they are also generally forgotten as part of the periictal amnesia. They can manifest as any of a number of learned motor behaviors, such as chewing, speaking, gesturing, walking, or making facial expressions. In severe complex partial seizures, they can be seen in the post-ictus as well. Automatisms can also be seen in primary generalized epilepsies, and they have limited role in localization; the guidelines do note that they are generally related to discharges in the limbic structures, but that the EEG takes precedence in localization over the presence and semiology of automatism.

Electrographically, the guidelines describe complex partial seizures as arising from unilateral or bilateral discharges frequently in the frontal or temporal regions. They can be focal or diffuse in distribution, though not overtly generalized. If there are bilateral interictal discharges, these are likely to be asynchronous.

### ***Partial Seizure Evolving into Secondarily Generalized Seizure***

Some partial seizures, whether simple or complex at onset, will evolve into a generalized seizure. The critical distinction between secondarily generalized seizures and primary generalized seizures is the focal origin with evolution to bilateral involvement. As with complex partial seizures, there is a loss of consciousness in the secondarily generalized seizure. Similarly, experiential symptoms, such as *déjà vu* or epigastric rising sensation preceding generalization, represent the original simple partial seizure and are considered aura. Characteristics of generalized seizures will be discussed subsequently.

### **Generalized Seizures**

Generalized seizures are defined by clinical and electrographic onset in both cerebral hemispheres, according to the 1981 nomenclature. Consciousness alterations are often the first presentation. The guidelines note that consciousness *may* be impaired; though, in clinical practice, impairment of consciousness in a generalized seizure is often assumed. Motor signs are bilateral. EEG findings will be bilateral and widespread at onset, differentiating these from partial seizures with secondary generalization.

Much as partial seizures are characterized by a mix of semiologic and EEG characteristics, so, too, are generalized seizures. The semiologic criteria are largely based on

automatisms and motor behavior, as consciousness is almost inevitably impaired. The 1981 recommendations divided generalized seizures into *absence*, *atypical absence*, *myoclonic*, *tonic*, *clonic*, *tonic-clonic*, and *atonic* or *astatic* seizures. As with partial events, generalized seizures can evolve into different behaviors during a given ictus. For example, it is not uncommon for absence seizures to evolve into tonic-clonic seizures; each phase of the generalized seizure can be identified individually by its subtype. Moreover, several seizure types can exist in the same patient, such as the constellation of absence, myoclonic, and tonic-clonic seizures in juvenile myoclonic epilepsy (JME). As in JME, these seizure categories are often tightly associated with specific epilepsy syndromes. These specific epilepsies and their criteria will be discussed in later chapters.

### Absence Seizures

Absence seizures are characterized by a sudden behavioral arrest. Ongoing behaviors, such as speaking, eating, or walking, will either markedly slow or stop, accompanied by a blank stare. The eyes may roll upward slightly. The patient will, at least initially, be unresponsive to stimuli. The seizure will end abruptly as well. In the *absence seizure with impairment of consciousness only*, these are the only clinical manifestations.

The 1981 guidelines allow for the typical absence seizure to be accompanied by several subtle phenomena seen in other generalized seizure types. These phenomena can be seen individually or in combination, and their guideline descriptions are summarized in the following. The *absence seizure with mild clonic components* has all the characteristics of altered consciousness noted earlier; however, there are clonic motions that can be seen, usually in the eyelids and mouth. When they involve the limbs, the patient can drop or throw objects held at the onset of the seizure. These clonic movements can manifest on a spectrum from the almost imperceptible to outright myoclonic jerks. *Absence seizures with mild atonic components* demonstrate minor losses in tone, leading to weakness usually in nuchal or trunk muscles, but sometimes also in the limbs. Unlike atonic seizures, where loss of tone can be sudden, these manifest as a drifting of limbs, neck, or trunk, and rarely as falls. *Absence seizures with tonic components* generate increased extensor or flexor tone in the neck, trunk, or limbs, and can cause back arching or retropulsion. *Absence seizures with automatisms* demonstrate automatisms comparable to those discussed with complex partial seizures. Indeed, in younger patients with new-onset epilepsy, absence seizures with automatism can be challenging to differentiate from complex partial seizures with automatisms on clinical grounds, often benefitting from EEG to differentiate. *Absence seizures with autonomic components* occur in conjunction with autonomic symptoms consistent with those discussed in simple partial seizures.

EEG criteria for absence seizures are a unifying feature. They consist of regular, rhythmic 2 to 4 Hz (classically, 3 Hz) spike-slow-wave discharges, which are bilateral and generally symmetric. The interictal EEG is generally normal,

with the exception of generalized burst phenomena, which can range from slowing to spike-wave activity.

### Atypical Absence Seizures

Atypical absence seizures are similar to typical absence seizures, but have both semiologic and electrographic aberrations. Clinically, they can have prolonged, or evolving onsets and endings, rather than beginning or ending abruptly as in typical absence. When tonic components are present, these, too, are more pronounced.

Electrographically, atypical absence seizures are defined by irregularity in the normally very rhythmic spike-slow-wave complexes, along with other high-frequency bursts and paroxysmal discharges. Seizures and paroxysms are often asymmetric, though still bilateral. There is more paroxysmal activity in the interictal EEG, often with asymmetric spikes and spike-slow-waves, and background activity is typically abnormal in these patients. The abnormal background is expected, given that atypical absence seizures usually are seen in patients who have multiple seizure types (eg, tonic and atonic) and have significant cognitive impairment.

### Myoclonic Seizures

Myoclonic seizures are sudden, short-duration contractions of muscles in the face, limbs, or trunk. They can be isolated, or occur in trains or clusters of jerks. Myoclonic jerks can be epileptic, relating to abnormal cortical activity, frequently in association with epilepsy syndromes, classically JME. However, myoclonus is frequently nonepileptic, arising from other sites in the central nervous system. Caution must be taken in diagnosing epileptiform myoclonus.

EEG findings associated with myoclonic seizures are typically polyspike-and-wave, spike-and-wave, or spike-slow-wave activity. Interictal EEGs can be normal, though tend to demonstrate interictal bursts of spike-wave or polyspike-wave activity.

### Tonic Seizures

Tonic seizures present with sudden and fixed contractions of limb, trunk, neck, and facial muscles. Contractions can be asymmetric, with eye and head deviation, and even turning of the body, along with uneven posturing of the limbs. As the muscles of the trunk contract, patients can become apneic, with pallor or cyanosis. Tonic activity can either be the principal semiology of a seizure, or occur as a phase in a longer ictus.

Electrographically, tonic activity generally appears as generalized alpha, or low-voltage fast activity, which increases in amplitude and decreases in frequency as the seizure evolves. Interictal EEGs are generally abnormal at baseline; spike-slow-wave discharges can be seen as well.

### Clonic Seizures

Clonic, like the term clonus, is derived from Greek, meaning “violent and confused motion.” It is rhythmic convulsive activity, consisting of successive, brief, high-amplitude limb

contractures, each followed by a relaxation phase. They tend to start at a high frequency, and then slow down as the seizure progresses, with preserved amplitude. Clonic seizures can occur in isolation, but typically occur as a phase in a longer generalized ictus.

Clonic seizures appear as alpha or beta frequency discharges, sometimes with spike-wave morphology. As the clonic motor activity slows, the EEG waveforms slow. The interictal EEG will frequently manifest spike-wave or polyspike bursts.

### *Tonic–Clonic Seizures*

As noted, tonic and clonic seizure activities are often phases of a more complex seizure. In the tonic–clonic seizure, classically called a *grand mal*, the seizure will begin with a tonic phase, which evolves into clonic activity. The tonic and clonic phases are consistent with the activity described in pure tonic or clonic seizures, and can frequently be accompanied by tongue biting and incontinence. The postictus can be profound, accompanied by somnolence, flaccidity, and prolonged confusion.

The tonic-phase EEG is accompanied by high alpha or beta frequency activity building in amplitude. With the clonic phase, the high-frequency activity is interrupted by a rhythmic spike-wave activity, which slows along with the clonic movements. A variant is the clonic–tonic–clonic seizure, which, as implied, starts with a clonic phase, progresses through a tonic phase, and concludes by returning to clonic activity. The interictal EEG is frequently abnormal, with polyspike-and-wave, spike, or spike-slow-wave activity.

### *Atonic (Astatic) Seizures*

Essentially a semiologic inverse of the tonic or clonic seizures, the atonic or astatic seizure is a sudden reduction or loss of muscle tone. They can be focal or generalized, involving the face, neck, trunk, or limbs. The onset can be gradual, leading to a progressive slumping or slouching. This slow-onset process can occur in a stepwise manner, as successive, rhythmic relaxations of the muscle groups. Fast-onset atonic seizures, the classic “drop-attack,” can lead to falls and head or neck injuries.

Atonic seizures are electrographically variable. They can appear as burst of polyspike activity or as electrodecrement, a flattening of the background, often after a generalized discharge. The interictal EEG is often abnormal, and can contain polyspikes, slow waves, and other generalized discharges.

### **Unclassified Epileptic Seizures**

At the time the 1981 recommendations were published, the authors recognized that many seizure types, often those seen in neonates, did not fit their classification scheme. These seizures were left undefined, with the understanding that further EEG and semiological data could eventually lead to their formal classification.

## **THE 2010 RECOMMENDATIONS FOR CLASSIFICATION OF SEIZURES**

The 1970 and 1981 proposals for seizure classification were a marked improvement over the more traditional terminology of *petite mal*, *grand mal*, and psychomotor epilepsy. Testing of the nomenclature in practice has shown promise, but some challenges as well. For example, it has been shown that even trained lay evaluators could accurately identify many seizure types, most reliably partial seizures, along with complex partial seizures and generalized tonic–clonic seizures. Interrater reliability was good between lay scorers and neurologists, though results were poor when scoring for simple partial, myoclonic, and atonic seizures (13). However, in the authors’ experience, there remains confusion regarding absence and complex-partial epilepsy among nonneurologists, and lay observers frequently default to more traditional *grand* and *petit mal* terminology.

Implementation and adoption aside, there are several technical problems with the electroclinical classification scheme. First, semiology and electrographic manifestations do not always directly correlate; this is especially true in frontal lobe seizures, which eluded precise clinical descriptions into the 1980s.

Furthermore, since electrographic and anatomical abnormalities did not always correlate, several prominent epileptologists argued that a purely semiologic nomenclature would be more appropriate (10,14,15).

Second, with improving structural and functional imaging, the classical distinction of a focal and generalized seizure became murky. The generalized seizure came to be seen as a focal process, rapidly conducted along a widespread, bilateral network of neurons; the partial seizure, conversely, originated from a focal region and spread more slowly, though not necessarily less widely, along different networks (15). With the idea of networked seizure propagation, the traditional dichotomy of a partial and generalized seizure was less reliable.

Third, the classification of partial seizures based off of alterations in consciousness was called into question. While, medico-legally, an alteration in consciousness has bearing on the ability to drive; it does not necessarily correlate with seizure severity or localization. Also, alterations in consciousness can be difficult to identify, particularly with ictal manifestations effecting individual components of consciousness. Returning to the operating definition, classification should be based off of meaningful differences between groups; to many epileptologists, it is unclear if altered mentation is a meaningful distinction (16).

In 2010, the ILAE Committee on Classification and Terminology issued revised guidelines on seizure and epilepsy nomenclature and classification. The greatest changes in the seizure nomenclature are for partial seizures, with a rejection of categorization by altered consciousness, and even a fundamental recasting of the definition of focal onset. Generalized seizure categories are spared heavy revision, though as with partial-onset seizures, there is a change in definition.



**TABLE 3.2 Summary of the 2010 Revised Terminology for Organization of Seizures**

Focal Seizures	Without impairment of consciousness		
	With impairment of consciousness; “ <i>dyscognitive</i> ”		
	Absence	Typical	
		Atypical	
		With special features	Eyelid myoclonia
		Myoclonic Absence	
Generalized Seizures	Myoclonic	Myoclonic	
		Myoclonic atonic	
		Myoclonic tonic	
	Tonic		
	Clonic		
	Atonic		
	Tonic–Clonic		
Unknown	Epileptic Spasms		

The catchall category of unclassified seizures has been reexamined, and epileptic (infantile) spasms are now specifically identified, whereas, in the 1981 recommendations, they are unrecognized. A description of these changes follows, and is summarized in Table 3.2 (15).

### Focal Seizures

The ILAE Commission on Classification and Terminology 2010 report redefines focal seizures. Previously, these were defined as seizures in which the initial clinical or electrographic findings suggested onset in one hemisphere. The updated guidelines are more conceptual, and describe focal seizures as abnormal electrical activity evolving within a local neural network that is, at least initially, confined to one hemisphere.

The commission concludes that there are insufficient data to support meaningful subdivisions in focal seizures. They abandon the concept of complexity, leaving all partial-onset seizures in the catchall category of *focal seizures*. Individual focal-onset seizures should be identified by semiology, and as before, description should include motor, sensory, autonomic, and psychic domains. For the sake of consistency, the commission encourages reference to the ILAE *Glossary of Descriptive Terminology for Ictal Semiology* (17). Despite the abandonment of the simple versus complex dichotomy, the commission recognizes the practical clinical importance of altered mentation in seizures. The guidelines encourage clinicians to address the issue of impaired consciousness. Seizures that would have previously been called complex should now be described as occurring “with impairment of consciousness or awareness,” or as “*dyscognitive*.”

### Generalized Seizures

Generalized seizures, like focal seizures, are redefined in terms of neural networks. The generalized seizure is defined as abnormal electrical behavior with onset in a network that rapidly conducts activity to both hemispheres. Onset can be cortical or subcortical.

Generalized seizures retain subcategories, which are felt to reflect meaningful clinical and pathophysiologic distinctions. These categories include *absence* (*typical*, *atypical*, or *with special features*), *myoclonic* (*myoclonic–tonic* or *atonic*), *clonic*, *tonic*, *atonic*, or *tonic–clonic* (of any combination).

#### Absence Seizures

The classification of absence seizures is changed minimally in the 2010 recommendations. The distinction between *typical* and *atypical* absence seizures remains, but they are both included in the same overarching category of *absence seizures*, not split into separate subcategories. The subcategory *absence with special features*, which includes *myoclonic absence* and *eyelid myoclonia*, is analogous to the 1981 guidelines’ descriptions of absence seizures accompanied by subtle clonic, tonic, or myoclonic components.

#### Myoclonic Seizures

Of the generalized seizure categories, myoclonic seizures show a greater degree of change. As described earlier, the 1981 guidelines parse myoclonic seizures broadly, as isolated or repetitive brief jerks, often seen in patients with other seizure types. The 2010 guidelines retain myoclonic seizures *per se*, but have also identified the subcategories of *myoclonic tonic* and *myoclonic atonic* seizures. As implied,

these seizures consist of a sentinel myoclonic jerk, followed by either a brief tonic phase or atony, respectively.

Subsequent commentary on the 2010 recommendations revise the associated EEG findings for myoclonic seizures as well, identifying them as spike-wave, or polyspike activity, followed by voltage attenuation (18).

### Clonic Seizures

There are no particular changes noted to this category of generalized seizure. As with the 1981 recommendations, clonic activity can be found independently or as a phase of a larger seizure.

### Tonic

As with clonic seizures, there are no significant changes reported for the category of tonic seizures. These, too, can be seen independently or as a phase of a greater ictus.

### Atonic

Atonic seizures have changed only limitedly: the 2010 guidelines now avoid the term *astatic*.

### Tonic–Clonic Seizures

Seizures involving any combination of tonic and clonic phases fit into this category. Aside from explicitly embracing all combinations of tonic and clonic behavior, this category is essentially unchanged from its 1981 description.

### Epileptic Spasms

Epileptic spasms, which are not part of the 1981 recommendations on seizure classification, are now specifically recognized. Commonly referred to as *infantile spasms*, the commission prefers the term *epileptic spasm*, because these may continue or arise after infancy. While warranting recognition as a specific seizure type, epileptic spasms remain in the *unknown* category, as there are insufficient data to assign them to either the focal- or generalized-onset groups.

Commentary on the 2010 guidelines identifies the expected EEG criteria for infantile spasms. This includes diffuse slow waves with subsequent electrodecrement, often followed by a reduction in interictal discharges (18).

### Unknown

The 2010 guidelines retain the unknown category, for any seizure types that cannot be identified as focal or generalized. The only named type in this category is the epileptic spasm, as mentioned earlier.

## COMMON USE

As of 2010, the ILAE has formally recommended the use of their new seizure classification and nomenclature. The 2010 recommendations have seen broader publication (18).

However, data are unavailable regarding the common use of the 2010 terminology. It is unclear the degree to which these guidelines are influencing the language of bedside practice.

In the authors' experience, both in general neurology practice and among epilepsy subspecialists, the 1981-era language of simple versus complex partial epilepsy remains prevalent. Outside of neurologists, older terminology such as *grand mal* and *petite mal* remains common, especially among nonclinicians.

## ILLUSTRATIVE CASES

The following are a series of brief cases intended to illustrate and compare features of the 1981 and 2010 seizure terminology. The intention of the discussion is purely didactic, not necessarily practical. For both sets of terminology, it is possible to generate complete, yet cumbersome descriptions of the seizure activity, which are rarely encountered at the bedside or in epilepsy conferences. Still, to understand the systems and their nomenclature, and identify their similarities and differences, it is instructive to apply the terms in context.

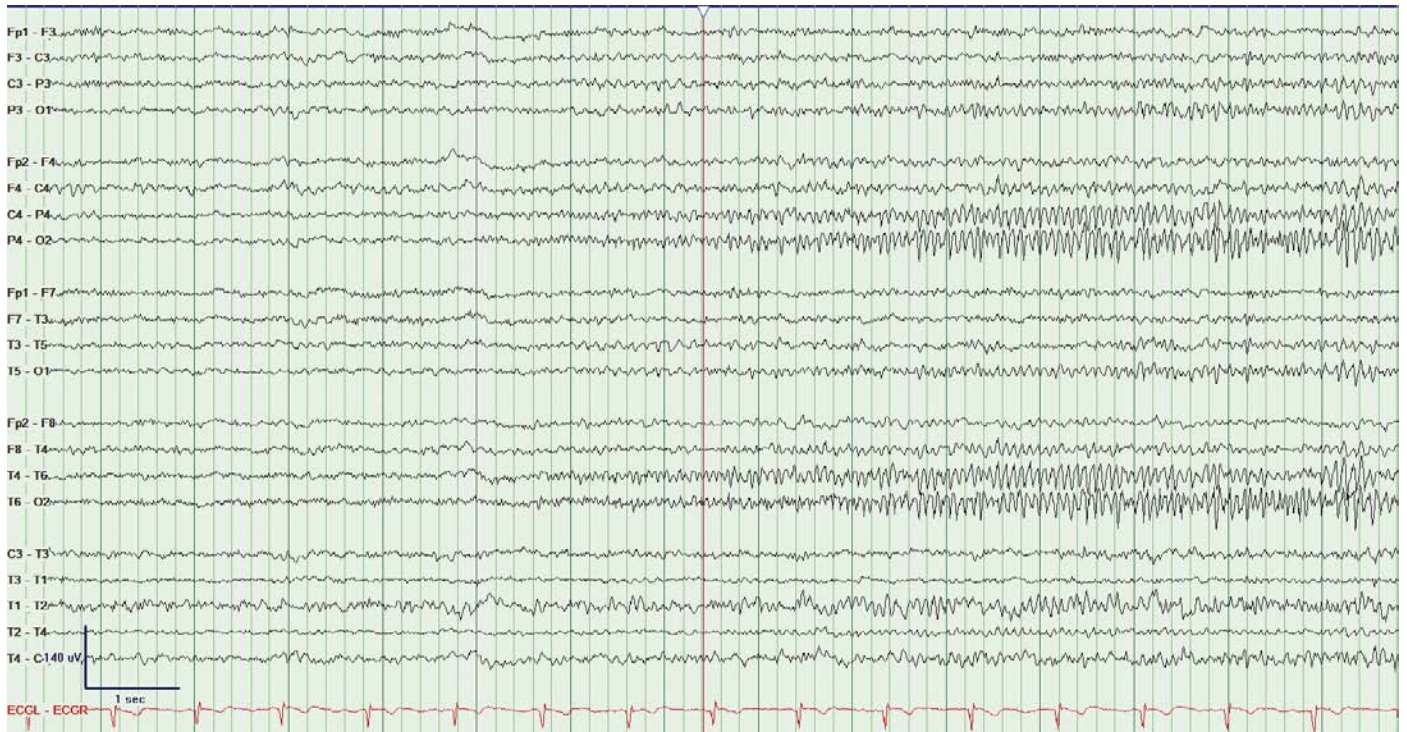
### Case 1

A 50-year-old male presents to a tertiary care hospital with a cluster of generalized tonic–clonic seizures. Bystanders and emergency medical services (EMS) staff were unable to describe seizure semiology prior to onset of convulsions. After recovering from a brief postictus and mild sedation from emergent benzodiazepines, the patient begins complaining of trouble with his vision. Nursing also notes that he has periods of left gaze preference with left head turning, though he will continue to converse and has no apparent loss of attention or responsiveness during these episodes. Physical examination is remarkable for a left homonymous hemianopia, and for several episodes of forced left gaze deviation and head turning, lasting approximately 90 seconds each. He is able to recall objects, respond to questions, and interact appropriately during these episodes. His MRI shows subtle diffusion restriction in his right occipital lobe along the calcarine fissure. vEEG is performed, and an EEG sample is displayed in Figure 3.1.

Despite his initial presentation with generalized seizure activity, the patient is currently suffering partial-onset seizures. As noted, he retains awareness and responsiveness during these events, which do not involve generalized activity, either by semiology or by EEG. In 1981 terms, these would be a simple partial seizure with focal motor signs. According to the 2010 recommendations, and with use of the 2001 *Glossary of Descriptive Terminology for Ictal Semiology*, these would be classified as focal versive seizures without dyscognition (17).

### Case 2

A 13-year-old female presents to the pediatric epilepsy clinic for evaluation of “staring spells.” For the past 9 months, the



**FIGURE 3.1** A 15-second epoch from an EEG from Case 1, in a longitudinal bipolar montage. Note the beta-frequency activity arising from the right posterior quadrant activity.

patient's parents have noticed that she will abruptly stop in the middle of a conversation, stare blankly, and then suddenly return back to the conversation. During longer episodes, her head will drop slightly, sometimes bobbing once or twice. She is otherwise well, performing at grade level in school, and her parents have no other concerns. She has a normal neurologic examination. Her MRI scan is normal. A routine EEG captures the finding shown in Figure 3.2.

This is a case of absence seizures, a finding supported by the patient's normal neurologic examination, normal MRI, and characteristic generalized discharges on EEG. Note, however, the parents describe atony with prolonged episodes, consisting of a mild, slow, head-drop. This is consistent, in 1981 terminology, with absence seizures with mild atonic components. In 2010 nomenclature, this is an absence seizure with special features. Despite the added atonic features in this case, this does not meet criteria for atypical absence in an otherwise normal teenager.

### Case 3

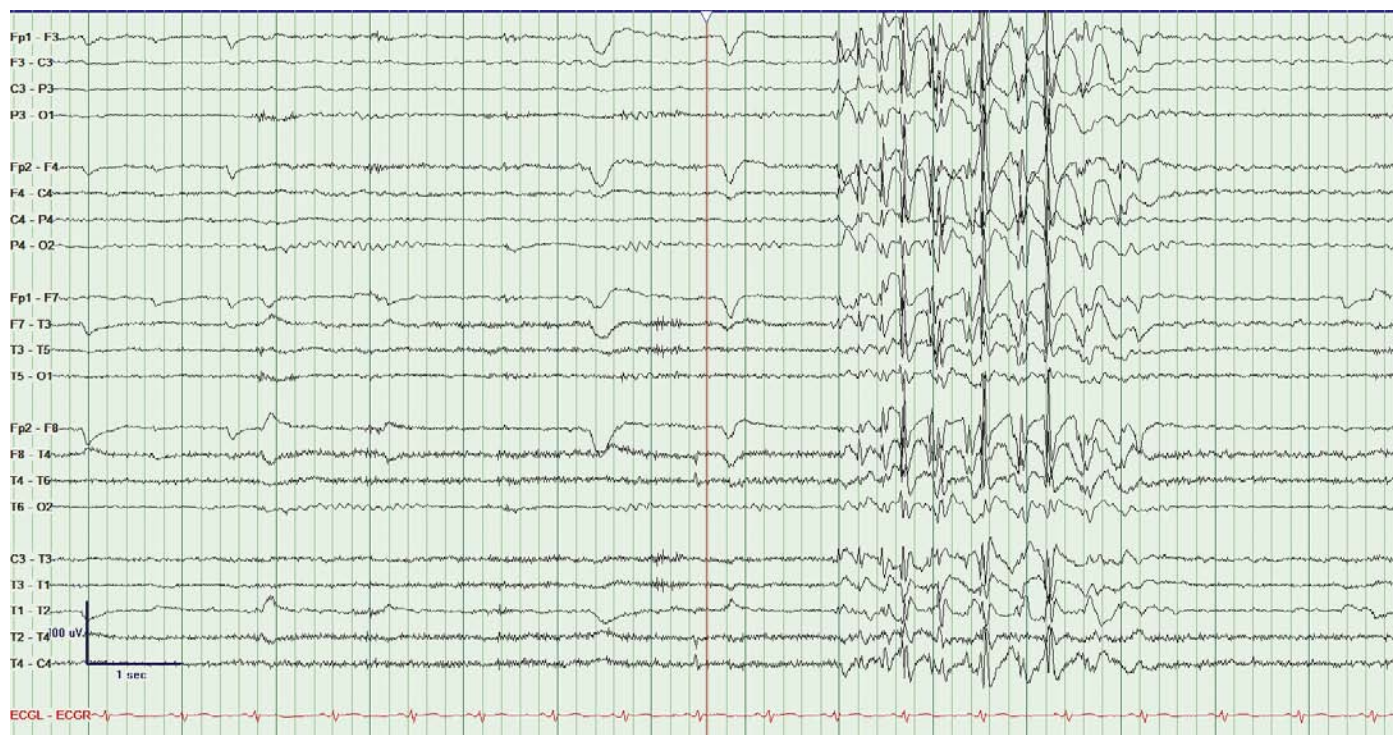
A 22-year-old man presents to clinic accompanied by his mother. He has had seizures since age 15 months, shortly after his grandmother reportedly dropped him on his head. His seizures consist of a sudden onset of staring, accompanied by repetitive muttering of comprehensible, but inappropriate words. His head then turns to the left, and his left arm extends outwards. These seizures frequently progress to

bilateral stiffening and then shaking, which lasts for 2 to 3 minutes. After cessation of the motor activity, he is unconscious for about 10 minutes, and fatigued for the rest of the day. He endorses, "feeling funny, kind of like I want to throw-up," before the seizures start. Occasionally, when he skips doses of his medications, he will feel that same funny sensation and nausea, but it does not progress into any other symptoms. His examination shows cognitive impairment, along with mild clumsiness and hyperreflexia of the left upper extremity. An MRI shows encephalomalacia in the region of his right temporal lobe. He undergoes vEEG as part of his workup. Figure 3.3 contains a segment of this tracing.

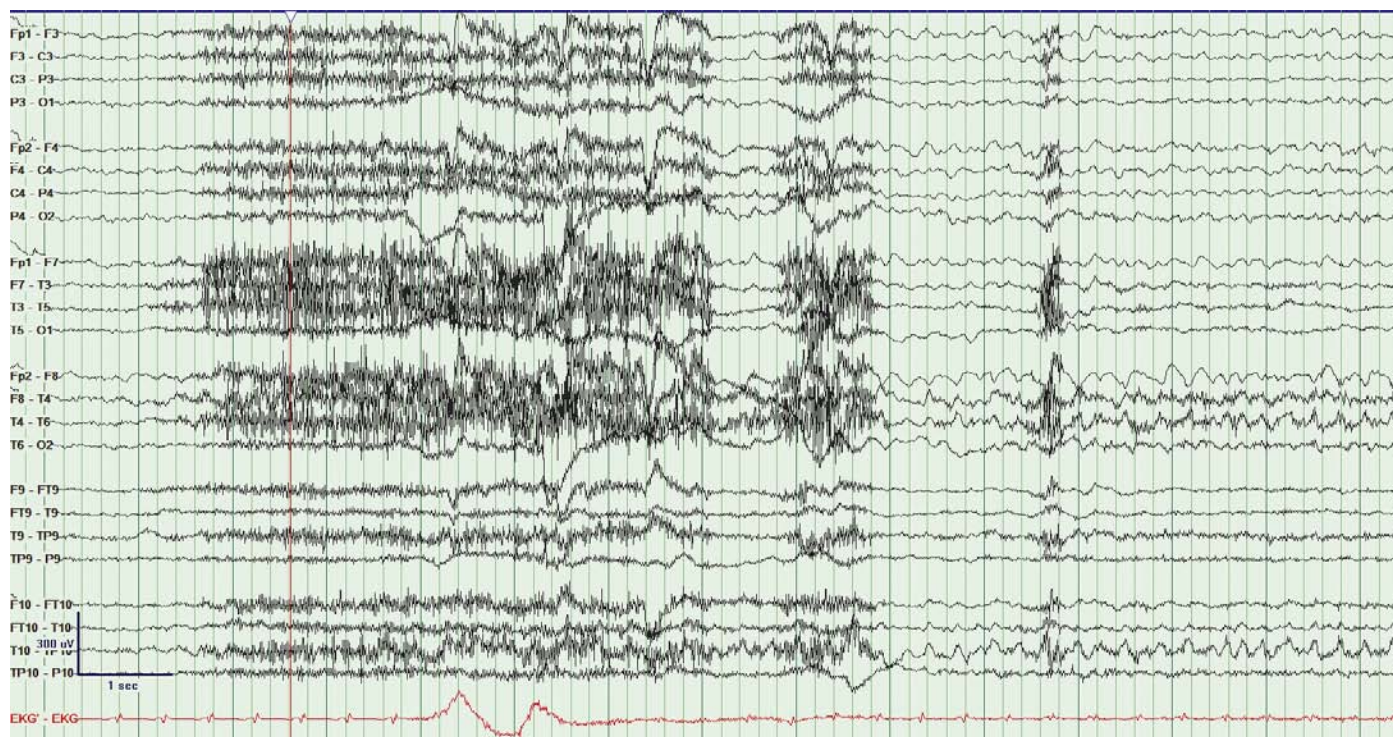
Based off of the semiology, focal examination findings, an MRI demonstrating temporal lobe pathology, and a vEEG demonstrating a focal onset from the right temporal region, this patient has localization-related epilepsy. This manifests with three related seizure types. The first seizure type is the sensation of nausea and a "feeling funny." Using older nomenclature, this is a simple partial seizure with subjective sensory symptoms. Contemporary nomenclature would prefer the term focal seizure without dyscognition and with epigastric symptoms. In either case, when it is recalled after one of his larger seizures, this becomes an aura.

When the seizure progresses to loss of consciousness, this would have previously been known as a complex partial seizure with simple partial onset. After 2010, a preferred description would be a focal dyscognitive seizure with aura, and with versive and tonic motor components.



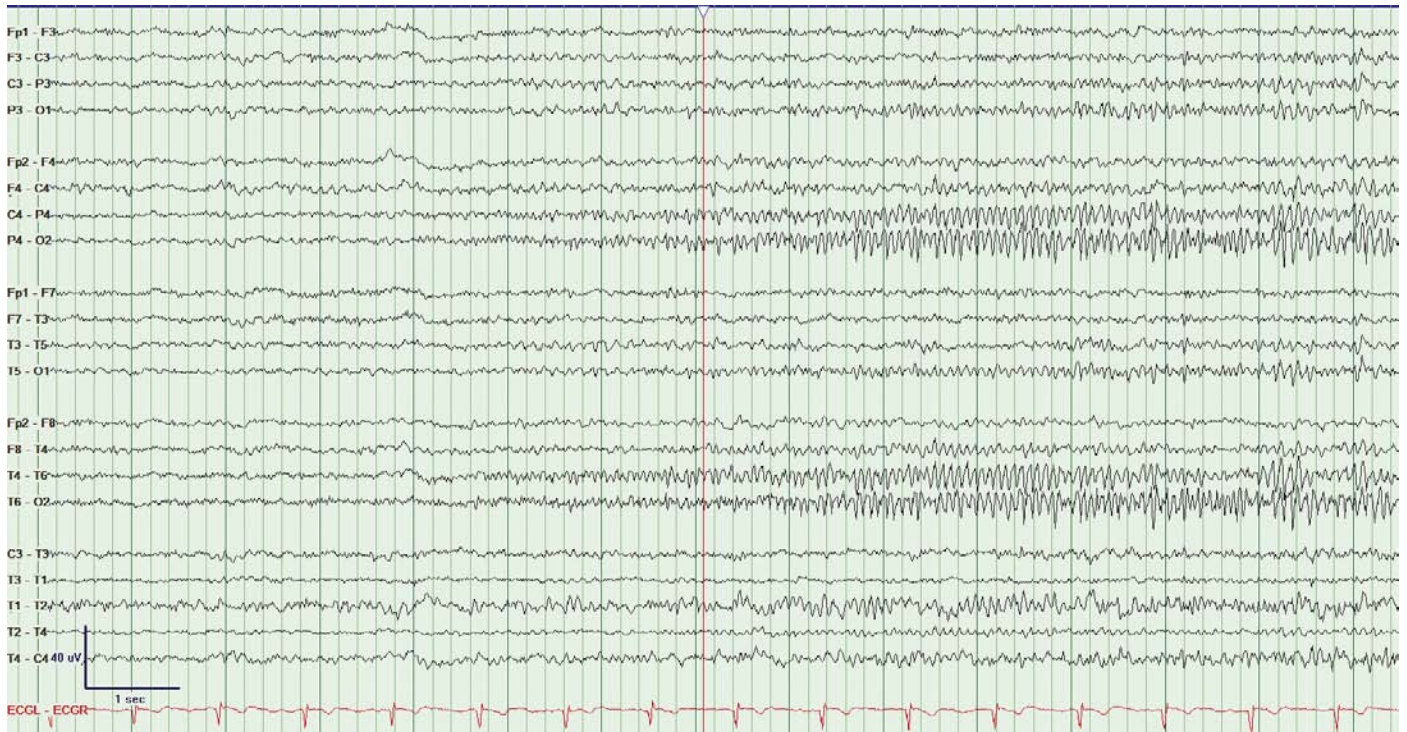


**FIGURE 3.2** A 15-second epoch from a routine EEG from Case 2, in a longitudinal bipolar montage, taken shortly after hyperventilation. The technologist present during the study did not note any clinical changes in the patient during the 3 Hz spike-wave burst.



**FIGURE 3.3** A 15-second EEG epoch from Case 3, in a longitudinal bipolar montage. It records the start of one of his seizures, shortly after he is noted to stare. Note the rhythmic 3.5–4 Hz activity arising principally out of the right temporal leads.





**FIGURE 3.4** A 15-second epoch from a routine EEG from Case 4, in a longitudinal bipolar montage, captured during an episode of repetitive closure of the patient's hand and flexion at the wrist, sparing the elbow and shoulder.

With the onset of generalized activity, beginning with a tonic phase and then developing clonic activity, the 1981-era description would be the following: simple partial seizures evolving to complex partial seizures evolving to generalized tonic-clonic seizures. Similarly, in 2010 terminology, this would be a focal dyscognitive seizure with aura, and versive and tonic motor components evolving to a bilateral convulsive seizure with tonic-clonic components.

### Case 4

A 60-year-old man presents to the clinic with 20 years of focal right arm twitching. The spells occur 10–20 times a day, and involve repetitive, brief pincer-like closure of his palm and flexion at the wrist, lasting 30 seconds at a time. Severe cases can involve additional jerking of his arm at the elbow, and rarely repetitive adduction at the shoulder. They can happen during wakefulness and sleep. He vehemently denies confusion during these episodes. They have remained refractory to multiple different antiepileptic agents, administered as monotherapy and in combination. His physical examination is remarkable for mild muscle hypertrophy of his right forearm, but subtle objective motor weakness in the right hand along with loss of coordination in his fingers. His MRI demonstrates an arterio-venous malformation occupying the left posterior frontal lobe. Functional MRI (fMRI) maps his hand motor area to within a centimeter of this vascular

lesion. The patient undergoes vEEG as part of his workup, and a portion of the record is seen in Figure 3.4.

This patient has repetitive, rhythmic episodes of focal motor activity, with preserved cognition. He has focal findings on his examination, consistent with a left-sided upper motor neuron injury, and a lesion on his MRI confirms it has cortical origin on the motor strip. While his ictal EEG shows some slowing over the left hemisphere, it shows no epileptiform activity. Per the 1981 guidelines, this picture is consistent with a simple partial motor seizure. The 1981 guidelines specify that focal motor seizures may not be captured on scalp EEG (5). This is a simple partial elementary motor seizure, because the closure of the hand and flexion at the wrist is an activity that could be simulated by direct stimulation of the hand and forearm flexor muscles. Using 2010 nomenclature, this could be described as a focal seizure with elementary motor components, without dyscognition.

Seizure classification and nomenclature have evolved dramatically since the 1960s. The ILAE Commission on Classification and Terminology played a critical role in developing two prevailing systems of seizure classification. The 1981 classification scheme was devised based on electroclinical and imaging findings from early vEEG and CT data. These guidelines fleshed out recommendations

dating back to the late 1960s, cementing the language of simple versus complex partial seizures, and defining partial and generalized seizures in terms of onset in one or both hemispheres, respectively. As imaging technology and more sophisticated EEG techniques evolved, some of the fundamental assumptions of the 1981 guidelines were called into question, such as the nature of partial versus generalized seizure onset and the utility of consciousness as criterion for classification. In response, new recommendations for seizure classification and terminology were issued in 2010, which eliminate subdivisions among partial-onset seizures, and recast the definition of focal and generalized seizures in terms of transmission along neural networks. Both systems can be used to identify and generate sophisticated descriptions of clinical seizures. Despite the effort to modernize the language of seizure classification, the 1981 classifications and nomenclature remain in common use, alongside the more contemporary 2010 recommendations.

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# Epilepsy Syndromes

*Richard P. Morse*

## 4

### C H A P T E R

#### CLASSIFICATION OF EPILEPTIC SYNDROMES AND THE EPILEPSIES

There are many reasons why classification of the epilepsies matters. A standardized classification and terminology for epileptic syndromes is needed for organizing and differentiating the epilepsies. The International League Against Epilepsy (ILAE)-standardized classification facilitates clinical practice, trials of seizure medications and other therapies, research and epidemiological studies of the epilepsies.

Historically, there have been multiple revisions of the classification schemes, and the process continues as scientific advances add to our understanding. Most recently, the impact of neuroradiology and neurogenetics has prompted attempts to revise the historical classification schemes. In this chapter, a brief historical overview is followed by terminology and definitions, principles considered by the committees charged with revising the classification, and presentation of the most current tables of the epilepsies. No classification system has yet emerged that is perfect and all encompassing, due to the competing needs of those using a classification system. There is a balance between a detailed, precise, and somewhat cumbersome classification system, and a clinically applicable, practical, and useful system that may oversimplify the complexity of the epilepsies and thus hinder our understanding. Nevertheless, for a system to be useful, certain compromises are inevitable.

#### HISTORICAL OVERVIEW

The International League Against Epilepsy (ILAE) has approached the classification of epileptic seizures and the epilepsies as a body from early on. The first meeting occurred in 1964 and led to a preliminary classification, which in turn was submitted to a Commission on Terminology for consideration. This commission published a proposed scheme of classification in *Epilepsia* in 1964. After additional input from neurologists, the proposal was reviewed again by the members of the Commission on Terminology in 1967, and a revised scheme of classification was published in 1969 (1), despite the lack of agreement in regard to certain terms.

Despite the limitations, the executive committee of the ILAE recommended the classification system be used in hopes of bringing more uniformity in the use of diagnostic terms, to facilitate the comparison of cases, and to improve methods of evaluating therapy and eventually further the understanding of the causes of epileptic seizures.

From the first publications in 1960 to the last official updates in 1981 and 1989 (Commission on Classification and Terminology of the ILAE, 1981, and Commission on Classification and Terminology of the ILAE 1989, Table 4.1), the classifications have been based largely on concepts and clinical observations, and did not include advances in neuroimaging, genetics, and pathophysiology at the molecular level. Other attempts have been made to update the 1989 and 1981 documents, including a task force report in 2006 (2), but it was not until the ILAE Commission on Classification and Terminology revision, which reflected the commission work from 2005 to 2009, was published in 2010, that an attempt was made to incorporate these advances in knowledge (3) (Table 4.2). The new classification scheme is based on revised concepts and terminology that reflect changes in the understanding of seizures and epilepsy. The authors of the revision used several guiding principles in approaching their task, and they realized that any classification scheme is incomplete and imperfect, and will change over time. They set forth a revised, simplified classification for seizures, but did not propose a comprehensive new classification of the epilepsies; rather, they grouped the epilepsies into categories that reflected the completeness of current knowledge about them. One important guiding principle was to strive for clarity and simplicity, so that terms would refer to single qualities and not reflect a mixture of different concepts and dimensions. Another important guiding principle was to not accept assumptions and assertions as the basis for classification, and to acknowledge areas lacking information for making appropriate decisions (4–6). Rather than classifying syndromes using the dichotomies of focal versus generalized, and idiopathic versus symptomatic, epileptic syndromes were characterized according to other features, including age of onset, cognitive and developmental antecedents and consequences, neurologic examination



**TABLE 4.1 International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders\***

<b>1. Localization-related</b> (focal, local, partial) epilepsies and syndromes	
<b>1.1 Idiopathic</b> (with age-related onset)	
1.1.1	Benign childhood epilepsy with central temporal spikes
1.1.2	Childhood epilepsy with occipital paroxysms
1.1.3	Primary reading epilepsy
<b>1.2 Symptomatic</b> (secondary)	
1.2.1	Temporal lobe epilepsies
1.2.2	Frontal lobe epilepsies
1.2.3	Parietal lobe epilepsies
1.2.4	Occipital lobe epilepsies
1.2.5	Chronic progressive epilepsy partialis continua of childhood (Kojewnikoff's syndrome)
1.2.6	Syndromes characterized by seizures with specific modes of precipitation
<b>1.3 Cryptogenic</b> , defined by seizure type, clinical features, etiology, anatomical localization, presumed to be symptomatic and of unknown etiology.	
<b>2. Generalized epilepsies and syndromes</b>	
<b>2.1 Idiopathic</b> (with age-related onset, listed in order of age)	
	Benign neonatal familial convulsions
	Benign neonatal convulsions
	Benign myoclonic epilepsy of infancy
	Childhood absence epilepsy (pyknolepsy)
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy (impulsive petit mal)
	Epilepsies with grand mal seizures (GTCS) on awakening
	Other generalized idiopathic epilepsies
	Epilepsies with seizures precipitated by specific modes of activation
<b>2.2 Cryptogenic or Symptomatic</b>	
	West syndrome (infantile spasms)
	Lennox-Gastaut syndrome
	Epilepsy with myoclonic-astatic seizures
	Epilepsy with myoclonic absences
<b>2.3 Symptomatic</b>	
2.3.1	Nonspecific etiology
	Early myoclonic encephalopathy
	Early infantile epileptic encephalopathy with suppression bursts
	Other symptomatic generalized epilepsies not defined above
2.3.2	Specific syndromes
	Epileptic seizures may complicate many disease states. Under this heading are included diseases in which seizures are presenting or predominant feature

**3. Epilepsies and syndromes undetermined whether focal or generalized****3.1 With both generalized and focal features**

Neonatal seizures

Severe myoclonic epilepsy and infancy

Epilepsy with continuous spike waves during slow-wave sleep

Acquired epileptic aphasia (Landau-Kleffner syndrome)

Other undetermined epilepsies

**3.2 Without unequivocal generalized or focal features****4. Special syndromes****4.1 Situation-related seizures**

Febrile convulsions

Isolated seizures or isolated status epilepticus

Seizures occurring only when there is an acute or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia

\*From Commission on Classification, Epilepsia 1989, with permission from John Wiley and Sons.

findings, EEG features, provoking or triggering factors, and patterns of seizure occurrence with respect to sleep. The defined categories that emerged from the most recent classification committee's work included:

- A. Electroclinical syndromes: It is a group of clinical entities reliably identified by a cluster of electroclinical characteristics.
- B. Constellations: On the basis of specific lesions or other causes, there are constellations but not electroclinical syndromes in the same sense. Diagnostically meaningful forms of epilepsy with implications for clinical treatment, particularly surgery. These include mesial temporal lobe epilepsy (with hippocampal sclerosis), hypothalamic hamartoma with gelastic seizures, epilepsy with hemiconvulsion and hemiplegia, and Rasmussen syndrome.
- C. Structural-metabolic epilepsies: These are secondary to specific structural or metabolic lesions or conditions.
- D. Epilepsies of unknown cause: Termed "cryptogenic" in the past, these are now referred to as "unknown" cause. "Unknown" is not considered a diagnosis (3–6).

## **EPILEPSY SYNDROMES/ ELECTROCLINICAL SYNDROMES**

An epilepsy syndrome is defined as a cluster of signs and symptoms that generally occur together. They also frequently indicate the anatomic or system localization of underlying known or suspected pathogenetic factors. Signs and symptoms may include the type of seizure, precipitating factors, severity, course, neurologic, EEG, and neuroradiologic findings, age of onset, and increasingly, genetic information. As

TABLE 4.2 Updated Classification of Epilepsies: Electroclinical Syndromes and Other Epilepsies\*

CLASSIFICATION	SYNDROME
<b>Electroclinical syndrome based on age at onset<sup>a</sup></b>	
Neonatal period	Benign familial neonatal epilepsy
	Early myoclonic encephalopathy
	Ohtahara syndrome
Infancy	Epilepsy of infancy with migrating focal seizures
	West syndrome
	Myoclonic epilepsy in infancy
	Benign infantile epilepsy
	Benign familial infantile epilepsy
	Dravet syndrome
	Myoclonic encephalopathy in nonprogressive disorders
Childhood	Febrile seizures plus (can start in infancy)
	Panayiotopoulos syndrome
	Epilepsy with myoclonic atonic (previously astatic) seizures
	Benign epilepsy with centrotemporal spikes
	Autosomal-dominant nocturnal frontal lobe epilepsy
	Late-onset childhood occipital epilepsy (Gastaut type)
	Epilepsy with myoclonic absences
	Lennox-Gastaut syndrome
	Epileptic encephalopathy with continuous spike-and-wave during sleep <sup>b</sup>
	Landau-Kleffner syndrome
Adolescence-Adult	Childhood absence epilepsy
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy
	Epilepsy with generalized tonic-clonic seizures alone
	Progressive myoclonus epilepsies (PMEs)
	Autosomal-dominant epilepsy with auditory features (ADEAF)
Less specific age relationship	Other familial temporal lobe epilepsies
	Familial focal epilepsy with variable foci (childhood to adult)
	Reflex epilepsies
<b>Distinctive constellations</b>	
	Mesial temporal lobe epilepsy with hippocampal sclerosis
	Rasmussen syndrome
	Gelastical seizures with hypothalamic hamartoma
	Hemiconvulsion-hemiplegia-epilepsy
	Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
<b>Epilepsies attributed to and organized by structural-metabolic causes</b>	
	Malformations of cortical development
	Neurocutaneous syndromes
	Tumor
	Infection

(continued)

**TABLE 4.2 Updated Classification of Epilepsies: Electroclinical Syndromes and Other Epilepsies\* (continued)**

CLASSIFICATION	SYNDROME
	Trauma
	Angioma
	Perinatal insults
	Stroke
	Etc.
<b>Epilepsies of unknown cause</b>	
<b>Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy, per se</b>	
	Benign neonatal seizures
	Febrile seizures

\*The arrangement of electroclinical syndromes does not reflect etiology.

<sup>b</sup>Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

\*From *ILAE Commission on Classification and Terminology, Epilepsia 2010*, with permission from John Wiley and Sons.

syndromes may have more than one cause, there can be a spectrum of the clinical features and there may be different outcomes. Some of the syndromes may be homogeneous and others more broad-based. There may be overlap of one syndrome into another, depending on the features that comprise the syndrome. Despite these inadequacies, the syndromic classification of the epilepsies remains useful. The following pages outline the major epilepsy syndromes in order of age of onset and serve as an overview but are not an attempt to be comprehensive. Anyone interested in epilepsy will need to keep current with ongoing investigations and discoveries, as new syndromes are added and established ones are revised. Resources for further reading are listed at the end of the chapter and include references (7–10).

## Electroclinical Syndromes Arranged by Age of Onset

### Neonatal Period

**Benign Familial Neonatal Seizures.** Benign familial neonatal seizures (BFNS) is an uncommon epileptic syndrome that involves generalized seizures in neonates and very young infants. Diagnosis is based on five criteria: (a) Onset of seizures during the neonatal period, (b) a normal neurologic examination, (c) exclusion of any other etiology of the seizures, (d) a positive family history of newborn or infantile seizures with benign outcome, and (e) normal developmental and intellectual outcome. The seizures typically begin during the first week of life, most often on the third day, but the onset in some instances may be later, after the first week. The seizures may occur quite frequently over a few days and then stop, or they may last a few weeks, but typically end within the first months of life. The infant tends to be normal during the interictal period. Clonic seizures, focal or multifocal, are the most frequent type; generalized seizures have been reported. Individual seizures last 1 to 2

minutes, but may occur 20 to 30 times a day. Linkage analysis in large families of patients with BFNS have demonstrated two loci for this autosomal dominant disorder, located on chromosomes 20q13.3 and 8q24. The genes encode voltage-gated potassium channels expressed in the brain (KCNQ2 and KCNQ3). The EEG is nonspecific and does not help in making the diagnosis of BFNS. Abnormalities have been reported on the EEG, including spikes, sharp waves, slowing, and others, but they do not distinguish the syndrome, and the EEG may be normal or have transient abnormalities. The patients have an excellent prognosis.

**Early Myoclonic Encephalopathy.** Early myoclonic encephalopathy (EME), or neonatal myoclonic encephalopathy, begins in the neonatal period. The seizures are variable in type, and include partial or fragmentary myoclonic seizures, massive myoclonia, partial motor seizures, and tonic seizures. The seizures of EME are often unresponsive to medication. The EEG shows a burst suppression or periodic profile, with bursts of spikes, sharp waves, and slow waves separated by suppression of the background. EME is associated with various etiologies, many of them metabolic, including nonketotic hyperglycinemia. Because of this, evaluation should include testing for inborn errors of metabolism. Infants with EME are usually severely neurologically impaired. More than half of them die before reaching one year of age.

**Ohtahara Syndrome.** Ohtahara syndrome is a rare epileptic syndrome with onset in the neonatal period, typically in the first two weeks, though it may begin earlier (in utero) or later, up to 3 months postnatal. Neurologically, these infants are abnormal. Ohtahara syndrome usually reflects a major brain malformation and has been associated with hemimegalencephaly, porencephaly, Aicardi syndrome,

linear nevus sebaceous syndrome, focal cortical dysplasia, and other brain malformations. It has only infrequently been associated with metabolic disorders. Seizures consist of tonic spasms with forward flexion lasting 1 to 10 seconds, that is, singular or in volleys that may recur hundreds of times a day. The spasms may be symmetrical, bilateral, or lateralized. They occur during wakefulness and sleep. A minority of neonates have multifocal clonic seizures. Unlike EME, in Ohtahara syndrome, myoclonic seizures are rare. Imaging usually shows severe developmental brain malformations. Metabolic screening is mandatory if brain imaging is normal. The EEG in Ohtahara syndrome typically shows an invariant burst suppression pattern with no normal features. Tonic spasms may correlate with the bursts of electrical activity on the EEG, or may be associated with diffuse attenuation, with disappearance of suppression burst activity during the spasm. Ohtahara syndrome is associated with high mortality and morbidity. Half of the patients die within months, and the others show profound developmental delay and major neurological deficits. There is no effective drug treatment for Ohtahara syndrome.

### Infancy

*Epilepsy of Infancy With Migrating Focal Seizures.* Epilepsy of infancy with migrating focal seizures is an infantile epileptic encephalopathy characterized by normal early development, refractory multifocal seizures arising independently from both hemispheres, and severe, progressive psychomotor retardation. In the revised ILAE terminology, it has been classified as an “electroclinical syndrome of unknown cause” with onset in infancy. Diagnostic criteria for epilepsy of infancy with migrating focal seizures include: (a) normal development before seizure onset, (b) onset before 6 months, (c) migrating focal motor seizures at onset, lasting for the first several months, often including autonomic manifestations such as apnea, cyanosis, or flushing, (d) multifocal seizures starting between 1 and 12 months that become intractable. Seizures tend to occur in daily multiple clusters, and may even be nearly continuous at times, (e) intractable to conventional antiseizure medications, (f) no identified etiology, and (g) profound psychomotor retardation, noted between 1 and 5 years of age. It is a rare syndrome and has been reported in a small number of infants. Although the seizures may become less frequent over time, there are frequent seizure recurrences during intercurrent illnesses. Outcome is poor, with global developmental delay.

*West Syndrome.* West syndrome (WS) is one of the pediatric age-related epileptic encephalopathies (11). The syndrome includes the triad of infantile spasms, an EEG showing hypsarrhythmia and psychomotor retardation. Infantile spasms (IS) occur only in infancy and early childhood. IS are myoclonic-like movements (sudden, brief) that usually begin in the first year of life, typically between 4 and 8 months, with 90% beginning under a year of age. Spasms can be flexor, extensor, or a mixture of both. The spasms primarily consist

of a sudden pitching forward from the waist with extension and stiffening of the arms and legs; some children have truncal extension rather than flexion. Various series give the incidence of mixed spasms at 40% to 50%, flexor spasms 35% to 40%, and extensor spasms 20% to 25%. Spasms tend to occur during state transitions, upon awakening or while falling asleep, and often occur in clusters. Infants may have dozens of clusters and hundreds of spasms per day. IS usually end by age 5, but other types of seizures often replace the spasms. WS leads to developmental regression and is associated with a specific EEG pattern known as hypsarrhythmia, which consists of high-amplitude, polymorphic delta, and multifocal and generalized spikes with a chaotic and disorganized background.

Many underlying causes and disorders, such as birth injury, metabolic disorders, and genetic disorders, can cause infantile spasms, which are more of an age-related manifestation of seizures than reflective of any specific cause. As there are many etiologies for IS, it is important to search for an underlying cause. About 10% of infants have no identifiable etiology. Almost any disorder causing brain damage can be associated with IS. Neonatal hypoxic ischemic brain injury is the most common cause. Other conditions associated with the development of IS include hydrocephalus, congenital or acquired microcephaly, brain malformations, Sturge-Weber syndrome, tuberous sclerosis, and other genetic syndromes (such as Aicardi syndrome, trisomy 21, other trisomies), prenatal/congenital infections, trauma, meningitis, encephalitis, intracranial hemorrhage, pyridoxine dependency (seizures may begin prenatally in this disorder), maple syrup urine disease, phenylketonuria, neurodegenerative diseases, biotinidase deficiency, and others. Increasingly, underlying genetic causes of IS are being identified. For example, MECP2 mutations, the cause of Rett syndrome in girls, have been associated with IS in affected males. Idiopathic IS are diagnosed if normal psychomotor development precedes the onset of symptoms; no underlying disorders or definite presumptive causes are present; and no neurological or neuroradiological abnormalities exist. If a cause presents itself, the syndrome is referred to as symptomatic WS, as the seizures manifest as a symptom of another problem. Almost any cause of brain damage can be associated with IS.

The pathophysiology mediating WS and IS remains unknown. There are hypotheses that the syndrome results from dysregulation of GABA transmission, or results from an overexpression of corticotropin-releasing hormone receptors. Various attempts to create an animal model have so far been unsuccessful at reliably reproducing infantile spasms.

Standard antiseizure medications are generally ineffective for treating IS. Adrenal corticotropin hormone (ACTH)/steroids and vigabatrin are the first-line drugs for this condition. ACTH is effective in 50% to 70% of cases. Alternatively, prednisone/prednisolone may be used; though studies have been hampered by a lack of dosing equivalencies when comparing ACTH to oral steroids. Vigabatrin has a response rate of about 50%, with a much higher response rate seen in infants with tuberous sclerosis. Other treatments include



benzodiazepines, valproic acid, lamotrigine, topiramate, zonisamide, and the ketogenic diet. In some patients, epilepsy surgery has been successful when the IS have been facilitated by the presence of a focal lesion.

Outcome depends on etiology. Early detection and prompt effective treatment have been shown to improve neurodevelopmental outcomes, especially in idiopathic cases. However, in most outcome series, between 70% and 90% of infants have psychomotor delay or regression (12).

*Myoclonic Epilepsy in Infancy.* Myoclonic epilepsy in infancy (MEI) accounts for about 2% of epilepsies that start before 3 years of age. Onset is 6 months to 3 years, and infants are neurologically normal. Seizures include myoclonic jerks, singular or in clusters. Consciousness most often remains normal during the seizures, but it may be affected during a longer cluster. Simple febrile seizures occur in 10% of these infants and other seizure types are not reported. About 20% have photosensitivity and another 10% may have stimulus-sensitive (sound or touch) seizures. Seizures tend to occur during transition from waking to sleep, and vice versa. The baseline EEG is usually normal, but during a seizure may show generalized polyspike and slow-wave or spike-wave discharges. Seizures are outgrown in the majority of infants within 1 to 2 years from onset. Up to 20% develop infrequent generalized tonic-clonic seizures in their early teens, and a similar number may have mild neurological deficits (cognitive, behavioral, or motor). EEG photosensitivity may continue after remission of seizures. Treatment with valproic acid has been most successful. Patients with acoustic and somatosensory-evoked myoclonus may not need treatment at all.

*Benign Infantile Epilepsy (BIE).* Benign infantile epilepsy (BIE) is also known as benign infantile seizures (BIS). Several types of BIE have been described. The ILAE classified the syndrome into familial and nonfamilial forms, though other forms have been described in the literature. Affected children, who have no other health or developmental problems, develop seizures during infancy. The seizures have a focal origin, but may spread to become generalized seizures. The seizures may occur several times a day, often groups in clusters over 1 to 3 days followed by a gap of 1 to 3 months. Treatment with antiseizure medications is not necessary but they are often prescribed and are effective at controlling the seizures. This form of epilepsy resolves after 1 or 2 years, and appears to be completely benign. The EEG of these children, between seizures, is normal. The brain appears normal on MRI scan.

The familial and nonfamilial forms have overlapping features and the presence of a family history of infantile seizures may be the only distinguishing criterion. The nonfamilial form has a larger range of the onset of seizures, from 3 to 20 months with most occurring between 5 and 6 months. With benign familial infantile epilepsy, the seizure onset is from 4 to 8 months of age.

*Benign Familial Infantile Epilepsy.* Benign familial infantile epilepsy (BFIE), also known as benign familial infantile seizures (BFIS), is an autosomal dominant (ie, genetic) epilepsy characterized by onset at age of 4 to 8 months. The neurologic prognosis is excellent. BFIS have been linked to chromosome 19q. Related infantile convulsions and choreoathetosis syndrome, in which BFIE are associated with paroxysmal choreoathetosis, have been linked to chromosome 16p12. Seizure types vary from simple partial seizures and complex partial seizures to generalized seizures beginning between 2 months and 2 years of age. Infants generally have normal neurologic examinations, and any neurologic studies are normal. There is no etiology identifiable. Family history is typically positive for seizures beginning at about the same age. Seizures tend to be brief and occur during the waking state, and are present in clusters in about half of patients. Interictal EEG is normal in nearly all infants.

*Dravet Syndrome.* Dravet syndrome (DS; also known as severe myoclonic epilepsy of infancy or SMEI) is a rare, genetic epileptic encephalopathy that begins in infancy. Seizures appear during the first year of life with prolonged febrile seizures or fever-related seizures. In the second year of life, afebrile seizures emerge, including myoclonic, eyelid myoclonia, absence, and generalized tonic-clonic. Susceptibility to hyperthermia-induced seizures persists, with febrile episodes often triggering status epilepticus. All seizure types may be prolonged or lead to status epilepticus. Seizures in DS are frequently resistant to treatment. The majority of children with DS show stimulus-provoked seizures, with a high degree of photosensitivity and emotional triggers (stress) being frequently observed.

Children with DS typically have developmental regression or delay, with developmental quotients in the 50 range (normal 100), with a high incidence of behavioral problems (hyperactivity, oppositionality) and disturbed sleep. Development is normal before the onset of afebrile seizures, as is the EEG during the first year. However, in the second year, development tends to arrest and subsequently may regress. The EEG changes in the second or third year of life, showing generalized spike, polyspike, and polyspike and slow-wave paroxysms. EEG studies should avoid using photic stimulation in these children due to the high risk of inducing a seizure.

As children with DS get older, their decline in cognitive function stabilizes, and in many, improves slightly. Neurologic impairment involves the development of ataxia and what is been termed "crouched gait." Severe learning disabilities are persistent. Seizures tend to be not only nocturnal but also persistent. There is a higher incidence of sudden unexpected death in epilepsy (SUDEP) associated with DS, with ongoing research into the possible association of the underlying channelopathy affecting the heart.

In more than 80% of cases, DS is caused by mutations in the SCN1A gene, the alpha subunit of a neuronal voltage-gated sodium channel. The sodium channel may



affect function of the inhibitory interneurons preferentially, leading to an imbalance between excitation and inhibition.

The drug stiripentol is considered the drug of choice for DS. It is typically used in combination with valproic acid and clobazam or another benzodiazepine. Stiripentol has been granted orphan drug status by the FDA, but is not generally available yet. The ketogenic diet has also been beneficial. For children with severe photosensitivity, specialized lenses may be of benefit. Certain antiseizure medications may exacerbate seizures and should be avoided, including carbamazepine, phenytoin, and lamotrigine (13).

*Myoclonic Encephalopathy in Nonprogressive Disorders.* Myoclonic encephalopathy in nonprogressive disorders (also termed myoclonic status epilepticus in nonprogressive encephalopathy, or MSNE) is characterized by early onset of repeated myoclonic status in infants and young children. The EEG shows continuous diffuse epileptiform abnormalities. The outcome from myoclonic encephalopathy is poor. This is a difficult-to-diagnose entity and needs to be distinguished from progressive myoclonic epilepsies and other infantile myoclonic epilepsies. Most often there is an underlying genetic defect, such as Angelman syndrome, history of hypoxic ischemic encephalopathy, or brain malformation. Seizure onset most often occurs around 1 to 2 years of age, with a range from 0 to 7 years.

### Childhood

*Febrile Seizures Plus.* Febrile seizures plus (FS+, generalized epilepsy with febrile seizures plus, GEFS+) refers to a genetic syndrome in which febrile seizures tend to start earlier than typical febrile seizures (less than 1 year) and persist longer than the usual 6 years. The syndrome is heterogeneous, and includes generalized epilepsy with febrile seizures plus (GEFS+). Children are neurologically normal otherwise, and may outgrow their epilepsy around age 10, or, in the case of GEFS+, may develop afebrile seizures (13%) including absence, myoclonic, atonic, or even focal seizures.

Because of a common genetic basis (primarily mutations in sodium channels, SCN1A and others) with DS, FS+/GEFS+ is considered a spectrum diagnosis by many. There is remarkable heterogeneity within this disorder, which has autosomal dominant inheritance with incomplete penetrance. EEGs range from normal to having generalized epileptiform discharges (spike-wave, polyspike wave). Development is normal or with mild disabilities. Treatment is standard for recurrent febrile seizures (rescue medication or “mini” prophylactic approach), and other seizure types are also treated in a standard manner, though the association with absence, myoclonic-astatic, and Dravet phenotypes suggests avoiding carbamazepine, lamotrigine, and phenytoin.

*Panayiotopoulos Syndrome.* Panayiotopoulos syndrome (PS) is the preferred name for what was previously termed “early-onset benign childhood occipital epilepsy.” PS accounts for up to 13% of 3 to 6 year olds and 6% of 1 to

14 year-olds with seizures. PS occurs only in children, and almost all seizures occur during sleep. A hallmark feature of PS is the prominent autonomic manifestations of the seizures, including vomiting, respiratory and temperature changes, pallor, mydriasis, urinary incontinence, and cardiac changes. Vomiting occurs in 75% of the seizures. Headache is also typical. Syncopal-like seizures with unresponsiveness and whole-body limpness are common. About half of the seizures end with convulsive activity. There is a great deal of variety in this epileptic syndrome. Seizures are described as typically prolonged, with more than half lasting more than 30 minutes, most often as autonomic status epilepticus. Despite the dramatic seizure, manifestation, and duration, the prognosis is excellent, the child typically returning to normal after a few hours of sleep. MRIs are normal. EEGs show marked variability, ranging from normal to multifocal spikes, and serial EEGs may change over time. Occipital spikes do occur but are not necessary for diagnosis. There may be frontal or central temporal spikes as well as generalized discharges. EEG abnormalities do not appear to be related to clinical course or prognosis. In PS, the cortical hyperexcitability is presumed maturational. PS is frequently misdiagnosed as a typical migraine, syncope, cyclic vomiting syndrome, or other nonepileptic disorders. Most patients have between one and five seizures, with only a third of patients having more than five seizures. The risk of developing epilepsy as an adult does not appear to be increased over the general population. Treatment is more likely needed for those children whose seizures are frequent, and there is no recommendation for any specific treatment that is likely to be superior.

*Epilepsy With Myoclonic Atonic Seizures.* This syndrome was previously known as myoclonic-astatic epilepsy or Doose syndrome. In this epilepsy, myoclonic atonic seizures are the defining symptom (100%), with symmetrical myoclonic jerks immediately followed by a loss of muscle tone. More than half of these children have brief absence seizures often associated with the atonic seizures. This epilepsy has its onset from 7 months to 6 years, peaking at 2 to 4 years. Affected children are neurologically normal prior to the onset of seizures. Seizures tend to be frequent, and tonic seizures are exclusion criteria (tonic seizures are a distinguishing feature of Lennox-Gastaut syndrome). In two-thirds, generalized tonic-clonic seizures may appear months before the myoclonic-astatic seizures, and one-third of these children are affected by nonconvulsive status epilepticus. EEGs usually show a normal background (again contrast to Lennox-Gastaut syndrome) with frequent generalized spike and polyspike and slow-wave discharges at a 2 to 3 Hz frequency. About half of the patients will outgrow their epilepsy and have normal development or minor neurologic impairment, and the remaining continue with seizures, more severe impairment of cognitive functions, and behavioral abnormalities. The most successful treatment has been with valproic acid, and levetiracetam, ethosuximide, clonazepam, or other benzodiazepines.

*Benign Epilepsy With Centrotemporal Spikes.* Also known as benign rolandic epilepsy, benign epilepsy with centrotemporal spikes (BECTS) represents the most common epileptic syndrome of childhood, affecting 15% of children. This epilepsy has an excellent prognosis. Seizures usually start between 4 and 9 years of age, with three-quarters identified being between 7 and 10 years. Seizures are infrequent (10% to 20% may have frequent seizures, but the majority have less than three), and they occur mainly during sleep (75%). The seizures consist of tongue and cheek numbness, hemifacial spasms or twitching, speech arrest or dysarthria, tongue and throat movements resulting in gagging or choking sounds, and hypersalivation. The seizures most often involve the face and arm, with less than 10% involving the leg. Consciousness is retained in up to 60% of patients. As the seizures occur during sleep, they may go unrecognized until they secondarily generalize and come to parental attention. Status epilepticus is rare. The EEG is characteristic, with a normal background and single or in a series centrotemporal spikes, which are markedly accentuated by sleep. There is often a horizontal dipole present (anterior–posterior rather than vertical to the brain surface). The frequency and persistence of centrotemporal spikes seen on the EEG do not have a bearing on the frequency of seizures or prognosis. This epilepsy is universally outgrown by 16 years of age, and the EEG likewise normalizes. Children with BECTS are neurologically normal, though there is a higher than expected incidence of learning disabilities when compared with children who do not have BECTS. There is a history of preceding febrile seizures in up to 20% of children with BECTS. A more malignant form of this epilepsy has been described with intractable seizures, developmental disabilities, and EEGs that may be along the spectrum of continuous spike waves during sleep, though this is exceptional.

Treatment may or may not be needed in this epileptic syndrome. Any antiseizure medication, preferably given as a once-daily nighttime dose, will usually control the seizures. Whether or not treatment of a centrotemporal spike (with or without seizures) found on an EEG will alter the learning profile remains the subject of great controversy and a much needed study.

*Autosomal Dominant Nocturnal Frontal Lobe Epilepsy.* Historically, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was one of the first epilepsies to have a genetic basis described (14). Inheritance is autosomal dominant with 70% penetrance. Linkage to the long arms of chromosomes 20 and 15 has been demonstrated, with mutations in genes encoding subunits of a neuronal nicotinic acetylcholine receptor causative of the epilepsy. ADNFLE has a markedly homogeneous clinical phenotype. In ADNFLE, seizures occur nearly exclusively during sleep (hypnagogic state or shortly before awakening). The seizures are hypermotoric, semiologically identical to seizures from the supplementary somatosensory area, occur frequently (often multiple times a night), and are brief (20–50 seconds). The hyperkinetic

movements are associated with dystonic posturing or tonic stiffening of the limbs and body, often with superimposed clonic components. Patients may be thrown out of bed and injuries may occur. Consciousness may be preserved. Secondarily generalized tonic–clonic seizures do occur in two-thirds of patients but are infrequent. Patients are neurologically normal, although there is an increased incidence of psychiatric disorders, likely due to the frequent misdiagnoses of the nocturnal seizures as a sleep disorder (benign nocturnal parasomnias, night terrors, and nightmares), obstructive sleep apnea syndrome, psychiatric or other medical disorder. Sleep is often fragmented because of the frequent nocturnal seizures, and thus excessive daytime somnolence is not uncommon. “Nocturnal paroxysmal dystonia” and “hypnic tonic postural seizures of frontal lobe origin” are diagnostic entities used in the past, which likely were given to patients with ADNFLE. Brain imaging is normal, as is the interictal EEG, though frontal lobe epileptiform abnormalities may occur in sleep. Interestingly, the ictal EEG is often not informative, or may show rhythmic slowing over the frontal region. Seizures tend to persist over the lifetime of the patient, waxing and waning in frequency, and ranging from mild to severe in an individual. The most common treatment used has been carbamazepine, but a number of patients may not respond, and alternatives include levetiracetam and lamotrigine.

*Late-Onset Childhood Occipital Epilepsy (Gastaut type).* Late-onset childhood occipital epilepsy (Gastaut type) is a childhood seizure susceptibility syndrome that has an age-related onset, is often age-limited, and may be genetically determined. Age of onset is 3 to 15 years, with a mean of around 8 years of age. Late-onset childhood occipital epilepsy (Gastaut type) accounts for between 2% and 7% of benign childhood focal seizure disorders. The seizures involve elementary visual hallucinations or loss of vision, occur frequently (daily, weekly), progress rapidly over a few seconds, and are brief—lasting from a few seconds to a few minutes, rarely lasting longer. Focal or generalized convulsive activity is less frequent (monthly, yearly), if it occurs at all. Elementary visual hallucinations (sparkling lights, flashes, multicolored circular patterns) are the most characteristic ictal symptom and may be the only clinical manifestation. Other occipital symptoms, including illusions of ocular movements and pain, tonic deviation of the eyes, eyelid fluttering, or repetitive blinking, may occur during the course of the seizures, as well, with eye deviation occurring in about 70%. Eye deviation may be associated with ipsilateral head turning and may culminate in hemiconvulsions and secondarily generalized seizures. In about 25% to 50%, the seizures are followed by a migrainous headache (diffuse or unilateral and pulsating, associated with nausea and vomiting). Ictal blindness may also occur, and usually has a duration of under 5 minutes. Consciousness is not impaired during the visual hallucinations or blindness, but may be impaired if the seizure progresses to a convulsive stage. The EEG

shows paroxysms of high-amplitude spike waves or sharp waves in the occipital (usually bilateral) and posterior temporal areas of one or both hemispheres, with a normal background. MRI is normal. The epilepsy is typically responsive to antiseizure medications and the prognosis is excellent, with 50% to 60% of patients outgrowing the epilepsy within 2 to 4 years after onset, and a significant minority continuing to have visual seizures and infrequent secondarily generalized tonic-clonic seizures.

*Epilepsy With Myoclonic Absences.* Epilepsy with myoclonic absences (EMA), also known as Tassinari syndrome, is rare and accounts for less than 1% of patients with epilepsy. Up to 70% of patients are male, a contrast to the female preponderance seen in childhood absence epilepsy. Although originally considered a symptomatic generalized epilepsy under the 1989 classification (due to the variable and often poor prognosis), EMA is currently considered among the idiopathic generalized epilepsies. This in part is because two types of EMA have been described, one with a more benign course and eventual disappearance of seizures (which tend to be exclusively myoclonic absence in type), the other with a poor prognosis, seen in patients who generally have myoclonic absence seizures in conjunction with other seizure types. About a third of the time there is an etiologic factor identified, including prematurity, perinatal brain injury, congenital hemiparesis, and chromosomal disorders, and these patients tend to have a poorer outcome.

Seizure onset ranges between 11 months and 12 years of age. Clinically, there are absence seizures with accompanying rhythmic bilateral myoclonic jerks, often severe. There is variable impairment of consciousness, and there may be apnea as well. The myoclonic movements involve shoulders, arms, and legs and last from 10 to 60 seconds, occurring many times a day. They may be precipitated by falling asleep or awakening. In about a third of patients, myoclonic absences are the only seizure type. Neurologic examination tends to be normal, though up to 45% will have a developmental disability of varying degree even before the onset of the epilepsy. Cognitive disabilities may worsen or even appear during the course of the epilepsy, in contrast to typical childhood absence epilepsy. The EEG usually has a normal background with generalized spike-wave discharges. During a seizure, there is a typical generalized 3 Hz spike wave, as seen in absence. In about a third of patients, the myoclonic absence seizures remit after about 5 years; the remaining two-thirds of patients continue with seizures. The duration of myoclonic absences has been tied to the likelihood of cognitive disability.

A subtype of EMA is eyelid myoclonia with absence epilepsy, also called Jeavons syndrome. The main seizure type is a brief absence, lasting less than 2 seconds, and associated with 4 to 6 Hz eyelid myoclonia, or eye rolling or jerking upward in a way that is distinctive from the typical eyelid fluttering that happens in childhood absence epilepsy. The seizures typically begin around 2 to 3 years of age, but due to their brevity (generally <10 seconds) may

go undiagnosed until later. Most patients have generalized tonic-clonic seizures during the course of their epilepsy. The seizures become quite frequent and may occur 30 or more times a day. There is a high degree of photosensitivity with light stimulus triggering seizures. Generalized tonic-clonic seizures are infrequent but may occur. Neurologic examination and outcome are normal in this epilepsy though seizures often persist into adult life. The EEG detects photosensitivity, and commonly polyspike discharges will be precipitated by eye closure. Fast (3 to 6 Hz) spike and polyspike and slow-wave generalized discharges may be recorded during seizures. The antiseizure medications, valproic acid, lamotrigine, and ethosuximide, are most helpful in management of these patients. Levetiracetam and clobazam may also be used. Carbamazepine, phenytoin, and vigabatrin should be avoided, as they may exacerbate the seizures.

*Lennox-Gastaut Syndrome.* Lennox-Gastaut syndrome (LGS) designates a syndrome with multiple types of seizures, especially tonic (stiffening), atonic (drop), and atypical absence. LGS is one of the age-related epileptic encephalopathies. Development is usually, but not always, impaired, and the onset of LGS may be associated with developmental regression or arrest. The EEG shows characteristic patterns of background slowing and spike-wave bursts at frequencies of less than 3 per second (slow spike wave). LGS accounts for 2% to 5% of childhood epilepsies, and typically appears between ages 2 and 5 years. There are many underlying causes of this condition, but in about 25% to 35% of cases, no cause can be identified. Lennox-Gastaut syndrome has been associated with perinatal brain injury, prematurity, infections (encephalitis/meningitis, prenatal TORCH [Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, and Herpes) infections, brain malformations, genetic disorders, and a preceding history of infantile spasms. These children are often normal at the time of seizure onset, but soon show psychomotor retardation in association with uncontrolled seizures. Behavioral problems are common. Nonconvulsive status epilepticus occurs not infrequently (spike wave stupor or prolonged atypical absence), as does convulsive status epilepticus. Most devastating are the tonic and atonic seizures, both of which place the patient at high risk for head injury from falls. Treatment is difficult, because the seizures tend to be resistant to antiseizure medications, and the intellectual changes do not respond to any currently available intervention. The epilepsy persists through adulthood, requiring long-term care and frequently institutional placement. Treatment has traditionally been with valproic acid, lamotrigine (often in combination with valproic acid), topiramate, felbamate, clonazepam, rufinamide, clobazam, and others, including the ketogenic diet. Vagal nerve stimulators are often used in patients with LGS, and there have been some encouraging reports of deep brain stimulation. For refractory drop attacks, corpus callosotomy may be of great benefit.



*Epileptic Encephalopathy With Continuous Spike Waves During Sleep.* Epileptic encephalopathy with continuous spike waves during sleep (CSWS) is an age-related and self-limited disorder characterized by epilepsy (with focal and generalized seizures), neuropsychological impairment with global or partial regression, transient motor impairments including ataxia, dystonia, dyspraxia, or unilateral deficits, and typical EEG findings comprising diffuse or unilateral electrical status epilepticus during slow-wave sleep, occupying up to 85% of the (slow-wave) sleep record. Clinical seizures may be absent or infrequent before the stage of electrical status epilepticus during slow-wave sleep. Clinical seizures are frequently nocturnal, focal motor, or secondarily generalized. CSWS is often associated with absence status, and although atonic seizures are not uncommon, tonic seizures do not occur in this syndrome. Peak onset is 4 to 7 years of age, with a natural history of 2 to 7 years, with remission of seizures and general improvement. Recovery is most often partial and slow, with less than 25% having a normal outcome. Those with a better outcome tend to have normal neurological profiles prior to onset of CSWS and have a shorter duration of the disorder. Although most patients (60%–75%) have a normal neuropsychological profile at the beginning of the disorder, there is a rapid cognitive and behavioral deterioration associated with the appearance of CSWS. In addition to the regression of intellectual ability, hyperactivity and aggressive behaviors have been observed as part of the encephalopathy. MRI is abnormal in more than half of patients, showing cerebral malformations, polymicrogyria, porencephaly, or various degrees of cortical atrophy. There is a high association with underlying genetic conditions, as well (example: ring 20 chromosome disorder). The EEG shows during the awake state typically multifocal spikes and synchronous frontal sharp waves, and with sleep shows continuous 1.5 to 2 Hz generalized spike-wave discharges during non-REM sleep. Successful treatment of CSWS has been elusive. Standard antiseizure medications, including valproic acid, levetiracetam, and high-dose diazepam (usually done in hospital with video EEG monitoring) have been tried, as well as, corticosteroids, intravenous immunoglobulin (IVIG), the ketogenic diet, and vagal nerve stimulation, but improvements of the EEG abnormalities may not correlate with improvements in the patient.

*Landau-Kleffner Syndrome.* Landau-Kleffner syndrome (LKS) is a rare childhood neurological disorder characterized by the sudden or gradual development of aphasia (receptive greater than expressive) in association with an abnormal EEG. The disorder usually appears between ages 5 and 7 years, with a preceding normal neurological profile and a progressive loss of language skills for no obvious reason. Many of the children have seizures but some do not. LKS is often misdiagnosed as autistic spectrum disorder, hearing impairment, learning disability, auditory/verbal processing disorder, mental retardation, emotional problems, or even attention deficit disorder. Treatment is difficult and often confers no benefit. Antiseizure medicines, corticosteroids, and multiple subpial

transections (MSTs) have been tried, but none of them is reliably effective. The prognosis for LKS is variable, with some children having a severe permanent language disturbance and others regaining their language skills, at least partly.

*Childhood Absence Epilepsy.* Childhood absence epilepsy (CAE) is an idiopathic generalized epilepsy occurring in otherwise normal children. Onset is between 4 and 10 years of age, with a peak of 5 to 7 years of age. Absence seizures are marked by an abrupt and complete behavioral arrest with impairment of consciousness. They last 4 to 20 seconds and can occur hundreds of times a day. The child will stare, sometimes blink, and there may be an associated mild loss of body tone and gentle clonic movements as the seizure ends. Absence seizures occur without aura and are not followed by any discernible postictal period. Automatisms are frequent as are mini rhythmic eye blinking movements (3 Hz). The EEG shows a generalized 3 Hz spike-wave pattern on a normal background. Hyperventilation will reliably provoke a seizure in the majority of children with CAE. The majority of children are neurologically normal, though school performance may be affected due to attentional deficits and slower processing speeds, attributable to the interictal, frequent subclinical discharges that may disrupt normal neuronal activity. About 50% of these children will have a generalized tonic-clonic seizure during the course of their epilepsy. The prognosis is excellent with seizures being outgrown in roughly 80% of patients, depending mostly on the age of onset.

### *Adolescence – Adults*

*Juvenile Absence Epilepsy.* Juvenile absence epilepsy (JAE) is in the spectrum of the absence epilepsies, with later age of onset (peaking between 9 to 13 years of age in 70% of patients) a much higher incidence of generalized tonic-clonic seizures, and a lower likelihood of outgrowing the epilepsy. There are myoclonic jerks in 20% of patients. The seizure type is predominantly typical absence, but they tend to be less frequent and of longer duration than in CAE. Seizures are often daily, lasting up to 30 seconds, and are longer than those seen in CAE. Children with JAE have a high rate of generalized tonic-clonic seizures over their lifetime, and are subject to absence status epilepticus /spike-wave stupor episodes, during which they may wander around and act confused. The epilepsy tends to be lifelong, but easily controlled with medication in the vast majority of patients (up to 80%). Seizures are precipitated by hyperventilation, sleep deprivation, fatigue, stress, and alcohol. The EEG shows a normal background with generalized spike and polyspike discharges, and the ictal EEG shows generalized 3 to 4 Hz spike or polyspike and slow-wave discharges. Valproic acid is the most effective antiseizure medication, with lamotrigine and levetiracetam as alternatives.

*Juvenile Myoclonic Epilepsy.* Juvenile myoclonic epilepsy (JME, also known as Janz syndrome) is included in the spectrum of the absence epilepsies, although it is distinguished by its

later age of onset, lifelong persistence, and high incidence of generalized tonic-clonic seizures. JME usually begins in late childhood or adolescence (8 to 20 years of age), and most typically is diagnosed in teenagers and young adults who experience their first seizure after sleep deprivation, the most potent trigger in this disorder. Myoclonic seizures are the most common type of seizure in this epilepsy, frequently occurring upon awakening. The patient may drop objects or experience myoclonic jerking of the upper extremities while remaining fully conscious. Generalized tonic-clonic seizures may ensue, and are most often triggered by a lack of sleep. Absence seizures also occur in less than 20%, again typically in the hours after awakening. JME accounts for about 5% of people with epilepsy, and has been associated with several different gene mutations that may cause or increase susceptibility to seizures. The inheritance pattern of at least one of these genes (GABRA1) is autosomal dominant, but complex inheritance patterns are suspected in other cases. Interestingly, most of the candidate genes code for ion channels. Patients are neurologically normal, as are imaging studies. The EEG in JME varies from normal to having generalized fast-spike wave or polyspike wave (3 to 5 Hz) discharges, particularly evident with drowsiness and sleep. There may be fragments of spike-wave on the waking EEG. About 20% of patients will have photosensitivity, and a small number will have a hyperventilation-induced seizure. Seizures tend to persist throughout the lifetime of the patient, though they are often quite easily controlled with antiseizure medication and avoidance of sleep deprivation. Valproic acid has been the drug of choice, but given concerns about reproductive health, especially in women (valproic acid is teratogenic and has been implicated in causing polycystic ovary syndrome), alternatives, including lamotrigine or levetiracetam, may be preferable.

*Epilepsy With Generalized Tonic-Clonic Seizures Alone.* The prevalence of this epileptic syndrome is unknown. It appears to be genetically determined and has shown linkage to the EJM1 locus for generalized tonic-clonic seizures on awakening, the best studied of the epilepsies grouped under this syndrome. By definition, all patients have generalized tonic-clonic seizures. These tend to occur within a few hours after awakening from sleep, but may also occur during relaxation or drowsiness. Seizure triggers include sleep deprivation, fatigue, stress, and alcohol consumption. The EEG is usually has a normal background with superimposed generalized spike and polyspike discharges in about half of the patients. About 15% have photosensitivity. The epilepsy tends to last for a lifetime with an 80+ percent likelihood of relapse on withdrawing treatment. Almost any of the antiseizure medications can be used, though for patients who have associated absence or myoclonic jerks as part of their epileptic manifestation, avoidance of carbamazepine, phenytoin, and oxcarbazepine is recommended.

*Progressive Myoclonus Epilepsies.* Progressive myoclonus epilepsies (PME) are rare and most often occur as part of

a neurodegenerative disorder. They typically involve both myoclonus (nonepileptic), tonic-clonic, and frequently myoclonic epileptic seizures. Other clinical features mainly rest on the underlying diagnosis, but typically involve progressive mental deterioration, cerebellar ataxia, and involuntary movements. The PME are seen in a variety of disorders, including mitochondrial disorders (myoclonic epilepsy and ragged red fibers), Unverricht-Lundborg syndrome (with Baltic and Mediterranean types), Lafora disease, Ramsay-Hunt syndrome (dentatorubral atrophy), sialidosis, Gaucher disease, and neuronal ceroid lipofuscinosis (NCL), especially the juvenile form. The PME are a heterogeneous group of disorders with very different clinical features, and only superficially similar, and such their classification as syndromic remains controversial.

*Autosomal Dominant Epilepsy With Auditory Features (ADEAF).* Autosomal dominant epilepsy with auditory features (ADEAF) includes autosomal dominant lateral temporal lobe epilepsy (ADLTE) and autosomal dominant partial epilepsy with auditory features (ADPEAF). ADEAF is characterized by autosomal dominant transmission, age of onset in late adolescence, focal and secondarily generalized tonic-clonic seizures with auditory hallucinations, no brain anatomic abnormality, and a good outcome. It has been linked to chromosome 10q22-24. Similar mutations have been described in a low percentage of patients with sporadic cases of idiopathic partial epilepsy with auditory features.

*Other Familial Temporal Lobe Epilepsies.* This designation reflects an emerging number of large pedigree/family genetic studies in which partial epilepsies, particularly of the temporal lobe, are found to have a genetic basis. As a group, these forms of epilepsy are found in otherwise neurologically normal individuals. Undoubtedly, as additional genetic information becomes available, this will be a rich source of understanding in terms of the pathophysiology of seizures, and will challenge the classification system in terms of the diversity of clinical expression and the genotype/phenotype correlation.

#### *Less Specific Age Relationships*

*Familial Focal Epilepsy With Variable Foci (Childhood to Adult).* Familial focal epilepsy with variable foci represents another subset of the inherited partial epilepsies. The clinical features of the seizures and the EEG interictal foci show great variability, with frontal, temporal, occipital, and central parietal seizures associated with corresponding foci on EEG. The main age of seizure onset is 12 to 14 years, although it can vary from infancy to middle age. Familial focal epilepsy with variable foci most likely has autosomal dominant inheritance. Patients are normal, neurologically, and have normal imaging studies.

*Reflex Epilepsies.* Reflex epilepsy is diagnosed when seizures are triggered by specific stimuli. The most

common reflex epilepsy is photosensitive epilepsy. Other stimuli include audiogenic, touch, and higher cognitive functions such as reading or writing. Most patients with reflex epilepsy also have other, spontaneous seizures. The seizure types provoked by stimuli may be generalized, including absence, myoclonus, or generalized tonic-clonic seizures, or focal, involving visual, motor, or sensory systems. Two patient groups experience reflex seizures: (a) a genetically determined group that is otherwise normal neurologically, and (b) a group that has severe brain injury with an inability to adequately inhibit excitatory sensory input to the central nervous system. In the symptomatic group of reflex seizures, startle epilepsy, with sound-sensitive seizures, is most commonly seen.

### Distinctive Constellations

#### *Mesial Temporal Lobe Epilepsy With Hippocampal Sclerosis*

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) is listed as a constellation rather than a syndrome, as it is a very common epilepsy seen in adults, has overlapping clinical features, is amenable to surgical management, but is heterogeneous as to etiology. There are familial forms of MTLE, and retrospective studies from surgical series have associated sporadic hippocampal sclerosis and MTLE development with preceding historical events such as febrile seizures, trauma, hypoxia, and intracranial infection, usually at an early age (less than 5 years). As HS has been demonstrated to develop over time, early identification of patients is difficult for studies of the natural history of HS. Data emerging from the febrile status epilepticus longitudinal multi-center study (FEBSTAT) supports an association between the occurrence of a prolonged febrile seizure in early childhood and the subsequent development of MTLE with HS. Whether there are additional genetic susceptibility factors involved or not remains to be determined, but they are strongly suspected. The seizure onset tends to be between ages 4 and 16 years of age for the majority of patients. The diagnosis is made when there is HS on MRI and a progressive course. Seizure semiology is typically that of a complex partial seizure with a preceding aura, mostly nausea or a rising epigastric sensation. The second most common aura is fear, either alone or accompanying the nausea. The seizure typically begins with a stare and oral alimentary automatisms, during which the patient is typically unresponsive. Dystonic posturing is contralateral, while automatisms are ipsilateral to the side of seizure onset. Early head deviation is ipsilateral, while head deviation later in the seizure is contralateral. Postictal aphasia reflects seizure origin in the language-dominant hemisphere. Seizures often become medically intractable. Precipitating factors include stress, sleep deprivation, and menstrual cycle-associated hormonal changes. Neurological profiles are typically normal, with the exception of memory deficits, which are often progressive.

#### *Rasmussen Syndrome*

Rasmussen syndrome (also called Rasmussen encephalitis, or RE) is a rare, progressive epileptic disorder that results in hemiatrophy of the brain, contralateral progressive hemiplegia, and cognitive deterioration, in association with intractable, progressive seizures. It most often begins in middle childhood and may have a protracted course punctuated with episodic status epilepticus. RE is associated with *epilepsia partialis continua*, an unusual form of seizure activity that may wax and wane over months or years, marked by arrhythmic twitching of a finger, toe, mouth, or other focal area. There is evidence to support that RE has an autoimmune basis rather than a genetic one. A viral etiology has been suggested by the pathology that includes cortical inflammation, neuronal loss, and gliosis confined to one hemisphere, and due to the similarity of RE to Russian spring summer meningoencephalitis, caused by a flavivirus. However, to date, there has been no viral agent identified. EEG tends to be abnormal, showing slowing and epileptiform discharges over the affected hemisphere; there may be no EEG correlate associated with *epilepsia partialis continua*. MRI shows progressive atrophy over the affected hemisphere, usually appearing and progressing within 6 months of the onset of seizures. Treatment is unsatisfactory, as the epilepsy rarely responds to medication. IVIG has been used as well as other immunomodulatory approaches, including chemotherapeutic agents, but the definitive intervention still remains (early) hemispherectomy.

#### *Gelastic Seizures With Hypothalamic Hamartoma*

This entity is listed as a constellation because of the high association of gelastic seizures (laughing seizures, often diabolical, forced laughter not affectively congruent) and hypothalamic hamartomas. Gelastic seizures can rarely come from other anatomical sites, such as the temporal lobe. Hypothalamic hamartomas can present with other seizure types in addition to gelastic seizures, most often complex partial seizures. The pathophysiology of seizures in hypothalamic hamartomas is not entirely understood, but intracranial monitoring studies have demonstrated that the seizures do originate and propagate from the hypothalamic hamartoma and adjacent structures.

#### *Hemiconvulsion-Hemiplegia-Epilepsy*

Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome refers to an outcome from focal status epilepticus, prolonged and usually febrile, in childhood. The syndrome is characterized by very long, usually unilateral clonic convulsions, though the activity may vary and involve both sides of the body (generally not synchronously), variable impairment of consciousness, and autonomic symptoms, including hypersalivation, cyanosis, and respiratory disorders. Acutely, there is hemiplegia and contralateral hemispheric swelling followed by cerebral hemiatrophy developing over weeks to months. The changes are not in a vascular territorial distribution, as seen in stroke. Clinical changes including



hemiplegia, visual field deficits, and language disturbance corresponding to the radiographic changes.

### **Epilepsies Attributed to and Organized by Structural-Metabolic Causes**

Epilepsy associated with trauma, stroke, brain tumors, metastases, autoimmune disorders, electrolyte imbalance, sepsis, CNS infection, neurodegenerative disorders, uremia, etc., varies from individual to individual and reflects the structural-metabolic underlying process. These epilepsies fall into the “symptomatic” category under the previous (1989) classification scheme.

#### ***Malformations of Cortical Development***

Malformations of cortical development include hemimegalencephaly, heterotopias, polymicrogyria, schizencephaly, lissencephaly, focal cortical dysplasia, types I and II, pachygyria, and others. Many brain malformations are highly epileptogenic. As there is a great deal of variety and unpredictability in how and whether a given malformation will be associated with epilepsy, it is more important to recognize the high frequency of brain malformations as a cause of epileptic seizures. Focal cortical dysplasia has emerged as a very common cause of focal seizures in children and frequently can be addressed surgically. Because of the high rate of malformations underlying epilepsy in children, MRI has become essential in the evaluation process.

#### ***Neurocutaneous Syndromes***

Neurocutaneous syndromes include tuberous sclerosis complex (TSC), Sturge-Weber, incontinentia pigmenti, neurofibromatosis, hypomelanosis of Ito, and linear nevus sebaceous syndrome. They are classically associated with an increased incidence of epilepsy, especially TSC. Each of the neurocutaneous syndromes involves clinical dermatological findings in association with CNS abnormalities. There is a great deal of variety in terms of the clinical presentation and findings. TSC is highly associated with infantile spasms in infants and typically has abnormalities on MRI that are diagnostic (multifocal cortical dysplasia called “tubers”) in addition to skin findings (hypopigmented macules, facial angiofibromata, ungual fibromata, shagreen patches). There are two genes (TSC1 and TSC2) identified in TSC, and their associated protein products, hamartin and tuberlin, respectively, act as tumor suppressor genes. The epileptogenicity of tubers is well understood and results from disruption of internal cell signaling pathways, as well as, neuronal connections within tubers and in the adjacent peri-tuber cortex. Sturge-Weber syndrome usually is identified because of a port-wine stain in the newborn that involves division I of the trigeminal nerve; MRI is diagnostic as it identifies the pial angiomas and progressive underlying cortical atrophy. Neurofibromatosis type I (NF-1), with multiple café au lait spots, neurofibromata, plexiform neuromas, and optic nerve gliomas, has an increased incidence of epilepsy over

the general population; up to 10% of patients have epilepsy for various reasons. Most of the neurocutaneous syndromes involve CNS structural/anatomic malformations as the cause of the epilepsy.

#### ***Tumor***

Brain tumors and metastatic tumors are both causes of recurrent seizures (epilepsy), usually considered symptomatic epilepsy. Generalizations are not of any great benefit, as the seizures reflect the site of origin and potential to spread to larger parts of the brain. Some brain tumors are quite epileptogenic, though, as a general rule, tumors do not tend to present with seizures in children, whereas in adults the two are commonly associated (about 50% of adults with brain tumors involving the hemispheres will experience seizures). However, gangliogliomas and developmental neuroectodermal tumors often present in childhood with seizures as their main manifestation. Hypothalamic hamartomas are another tumor highly associated with epilepsy. There is a growing awareness of subclinical seizures that may be associated with brain tumors, and the treatment of tumors (surgery, radiation, chemotherapy) may contribute to the development of epilepsy as well.

#### ***Infection***

CNS infections, including encephalitis and meningitis/meningoencephalitis, vasculitis, are all associated with a high risk of seizures, and postinfectious epilepsy occurs at an overall increased rate. Encephalitis carries about a 20% risk of developing epilepsy, and meningitis about half of that, if there are seizures during the acute illness. If there are no acute seizures, the risks are much lower, about 10% for encephalitis and 2.5% for meningitis. Acute seizures in the course of a CNS infection are considered provoked, symptomatic, and not epilepsy, but late-occurring seizures are considered unprovoked and more likely associated with epilepsy.

#### ***Trauma***

There is a high rate of seizures associated with traumatic brain injury. Seizures may occur immediately, within the first week, and after the first week, and are termed early or late, accordingly. The risk of developing epilepsy is greatest if there are late seizures, though a single late seizure may warrant observation rather than treatment. Early seizures (including immediate) are generally not considered as likely to be associated with the development of epilepsy; rather, they are considered symptomatic seizures. In both civilian and military studies, severe brain injuries with focal intracranial lesions, fractures, or prolonged alteration in consciousness are the most important risk factors for development of posttraumatic seizures. Traumatic brain-injured patients are often treated with prophylactic antiseizure medications, with the assumption that treatment will lower the likelihood of developing posttraumatic epilepsy. However, studies have shown that antiseizure medications only prevent

early posttraumatic seizures. Antiseizure medications are of no benefit in preventing late posttraumatic seizures. On the basis of these data, patients with severe traumatic brain injury should receive preventive treatment with antiseizure medication (usually phenytoin) as soon as possible after injury, but for no longer than a week.

### *Angioma and Other Vascular Lesions*

Arteriovenous malformations (AVMs), developmental venous malformations (DVMs), and cavernous angiomas, are all associated with an increased risk of epilepsy, both due to their tendency to bleed and due to peri-lesion associated brain malformations. The epilepsy typically involves partial seizures reflecting the anatomy.

### *Perinatal Insults*

Neonatal hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures, but subarachnoid hemorrhage, intracranial hemorrhage, infection, hypoglycemia, electrolyte abnormalities, and iatrogenic are also causes of seizures in the newborn, with an increased risk of epilepsy. Neonatal seizures are further discussed in Chapter 5.

### *Stroke*

Cerebrovascular diseases, including strokes, have long been recognized as a risk factor for the development of epilepsy, particularly in elderly populations. Hemorrhagic stroke is far more likely to cause seizures. Poststroke seizures are estimated to affect 22% of patients who have had a stroke, the majority occurring in the first month after a stroke; later occurrence of seizures carries a higher risk of recurrent seizures (epilepsy). There is a high frequency of peri-stroke clinical and subclinical seizures noted with monitoring. Patients with intracranial hemorrhage have the highest incidence of seizures—8.4 percent—in the first 24 hours after stroke. There are various estimates of the frequency of seizures in stroke, with a range of ischemic stroke up to 10%, intracranial hemorrhage up to 25%, and subarachnoid hemorrhage up to 35%. The development of epilepsy after a stroke is much lower, affecting 3% to 4% of patients overall, but among the elderly, stroke (vascular disease) is the primary cause of new-onset epilepsy.

Other cerebrovascular conditions predispose to stroke and seizures, and may be the cause of epilepsy. Moyamoya disease is a progressive obliteration of the intracranial carotid artery that has both genetic and acquired forms; seizures are usually stroke-associated. CNS vasculitis and sickle cell disease have an increased risk of subarachnoid hemorrhage and stroke, both associated with seizures and increased risk for the development of epilepsy.

### *Metabolic Disorders*

Metabolic disorders encompass a growing number of epilepsies that result from inborn errors of metabolism, including glucose transporter 1 (GLUT1) deficiency syndrome, mitochondrial respiratory chain deficiencies, pyruvate

dehydrogenase deficiency, sulfite oxidase/molybdenum cofactor deficiency, guanidinoacetate methyltransferase deficiency, NCL, and biotinidase deficiency, to name a few (15). Metabolic disorders that present in infancy tend to have seizures more often than when they present later in life. The seizure types are nonspecific, often generalized, though this will depend on the age of the patient and the specific disorder. GLUC1 syndrome, which is marked by low CSF/CNS glucose, is highly associated with early life intractable seizures and responds dramatically in most cases to the ketogenic diet. A gene test is now available to diagnose it (SCL2A1 gene); CSF studies typically show a low glucose and lactate. Pyridoxine-dependency is another important and eminently treatable epilepsy due to an inability to synthesize adequate amounts of the active form of vitamin B6 (pyridoxine). Affected infants may have seizures beginning in utero, and seizures typically have their onset in the neonatal period, though there are reports of later onset. Treatment with daily pyridoxine is sufficient to control the seizures. The gene has been identified and testing is available (ALDH7A1). The mitochondrial disorders represent an emerging and important area of childhood epilepsies, with myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) being two of the more well-characterized disorders. Alper's syndrome and Leigh's disease are additional disorders with a mitochondrial basis that often start in infancy and involve severe developmental regression and seizures. There are genetic tests available for the more common mitochondrial disorders.

### *Autoimmune*

Autoimmune disorders are increasingly being recognized as a cause of epilepsy. Autoimmune conditions associated with increased incidence of epilepsy include systemic lupus erythematosus, thyroiditis (Hashimoto's encephalopathy), diabetes mellitus, Crohn's disease, celiac disease, Henoch-Schönlein purpura, and others. In addition, the paraneoplastic syndromes represent another autoimmune-mediated form of epilepsy. Antibodies to *N*-methyl-D-aspartate (NMDA) receptors have been associated with a severe form of encephalitis that often presents subacutely with psychiatric symptoms and less commonly with short-term memory deficits; seizures are frequent, including status epilepticus, clinical and subclinical. Other paraneoplastic syndromes are associated with brainstem or limbic encephalitis and may involve subclinical status epilepticus and seizures.

### **Epilepsies of Unknown Cause**

No single feature or group of features is currently known to provide helpful information for treatment, management, and prediction of prognosis for these undifferentiated epilepsies. There are many epilepsies that which will be placed in this category, and it does not serve as a diagnosis at this point.

## Conditions With Epileptic Seizures That Are Traditionally not Diagnosed as a Form of Epilepsy per se

### Benign Neonatal Seizures

Benign neonatal seizures (BNS) are defined as seizures with onset after birth through day 28 in an otherwise healthy child with no other known medical or neurologic problems. Such cases may be familial or isolated. Psychomotor development should be normal for a full-term or near-full-term infant with benign convulsions. Between seizures, findings on neurologic examination should be normal. Clinically, the seizures are frequent and brief, occasionally occurring many times within a day. BNS have been called “fifth day fits” after the likelihood of the seizures occurring then. BNS is rare, and must be distinguished from BFNC; BNS has a higher rate of status epilepticus and also has an EEG pattern known as trace pointu alternant. This pattern is frequently reported but not exclusively found in BNS, and consists of persistent discontinuous theta activity with intermixed sharp waves that are unreactive and often asynchronous. The pattern occurs in all states and it may persist until the 12th day of life, even after the seizures have ceased. The seizures usually last only a few days but may continue for a few months. Neurologic outcome is normal.

### Febrile Seizures

Febrile seizures (FS) are very common, affecting up to 5% of children between 6 months and 6 years, peaking at 14 to 16 months. This is not considered epilepsy but an age-related susceptibility and an expression of symptomatic seizures. Febrile seizures are classified as simple or complicated, the former carrying only a slightly increased risk of epilepsy, about two times that of the general population. Complicated febrile seizures can be associated with an increased risk of epilepsy and generally warrant additional investigation. A simple febrile seizure is defined as one that is generalized, lasts less than 15 minutes, and occurs as an isolated, single event during a febrile illness. Complicated febrile seizures are defined as focal, lasting longer than 15 minutes, and recurrent within a febrile illness. Each of the features carries increased risk of developing afebrile seizures/epilepsy. In addition, prolonged febrile seizures (status epilepticus, defined historically as seizures >30 minutes) have been associated with subsequent development of temporal lobe epilepsy with mesial temporal sclerosis in a subset of children (16). Most children with febrile seizures, even complicated febrile seizures, require no treatment. Rectal benzodiazepines may be offered for seizures more than 5

minutes and recurrent febrile seizures may be treated with a “mini-preventive” approach using an oral benzodiazepine for 48 to 72 hours. Chronic antiseizure treatment should be reserved for those children diagnosed with epilepsy.

The classification of epileptic syndromes and epilepsies continues to evolve. The ILAE’s newest classification incorporates new knowledge of neuroimaging, genetics, and pathophysiology. In this classification, the epilepsies are grouped into categories that reflect our current understanding. An overview of the various epilepsies according to the current classification has been presented in this chapter. As the knowledge about these conditions increases, the classification will require further modification in the future.

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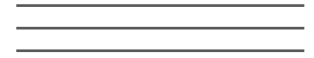
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# Neonatal Seizures

*William B. Gallentine*

## 5

### CHAPTER



Seizures occur frequently in the newborn period, more commonly than in any other time period across the lifespan. They have been associated with increased mortality, adverse neurodevelopmental outcome, and increased risk of epilepsy later in life. Frequently, seizures in neonates are only detected by EEG as clear clinical behavior is often absent. This, along with the high rate of nonepileptic paroxysmal behaviors, makes continuous EEG monitoring imperative in the management of these patients. It is important to delineate the underlying etiology of neonatal seizures, as this often carries the greatest implications in regard to prognosis. It is very important to recognize that some etiologies do have specific disease-altering therapies, which can have profound impacts on outcome. Although these disorders are relatively rare, care should be taken not to miss them as the consequences in terms of neurologic sequelae can be great. Overall, current therapeutic options for neonatal seizures are quite limited. As such, there is a significant need for further studies in this area.

#### DIFFERENTIAL DIAGNOSIS

There are many paroxysmal nonepileptic behaviors that can occur in the neonate, which may be misinterpreted as clinical seizure activity. Table 5.1 provides a list of behaviors that may mimic seizures along with their distinguishing features. Continuous EEG monitoring is helpful in clarifying the nature of these events and prevents overtreatment with antiepileptic drugs. In a child that is stable and not having clear epileptic events, if EEG can be obtained in a timely manner, delaying treatment for EEG confirmation is reasonable. Clinical behaviors that have a high correlation with electrographic seizure activity include recurrent rhythmic focal clonic activity and tonic gaze deviation, with or without associated nystagmus. Generalized tonic posturing is rarely associated with electrographic seizure activity, but often mistaken for seizure. Apnea associated with tachycardia is much more likely to be associated with seizure, rather than that of bradycardia.

Although apnea is much more likely to be nonepileptic in etiology, it can be a sole seizure manifestation. Because these behaviors can be so difficult to clinically distinguish from seizure activity, continuous EEG monitoring is essential for activity characterization. Ultimately, less than half of the behaviors initially concerning for seizures in the neonatal intensive care unit are confirmed to be seizures by EEG.

#### EPIDEMIOLOGY AND RISK FACTORS

The true incidence of neonatal seizure has been difficult to estimate and varies greatly depending on the study. Traditionally, seizure incidence was reported based upon clinically observed abnormal behavior, without EEG. This premise has proven to be flawed, as it is now well known that many of the seizures occurring in this patient population are electrographic only. Thus, studies using clinical observation have grossly underestimated the true incidence. There is also a high rate of nonepileptic events that may be mistaken for clinical seizures without EEG confirmation. Prospective studies using continuous EEG monitoring are currently lacking and are needed to define the true incidence. Clinical seizure activity has been reported in 0.95–5.0/1000 and 13.5–57.5/1000 very-low-birth weight live births (1). Risk factors associated with seizures in neonates are listed in Table 5.2 (1,2).

EEG background patterns have proven to be a powerful tool in predicting both seizures and outcome in critically ill neonates. As it is important to recognize the normal EEG changes occurring every few weeks in the preterm infant in order to provide accurate background assessment, the normal maturation of the preterm infant EEG is discussed in Table 5.3. Mild (excessive discontinuity) to severe (burst suppression) EEG background abnormalities have been shown to be predictive of electrographic seizures (Table 5.2) (2). In general, isolated spikes and sharps in the neonatal EEG are not predictive of neonatal seizures, and only represent diffuse brain dysfunction.



**TABLE 5.1 Differential Diagnosis of Paroxysmal Nonepileptic Behaviors in the Neonate**

BEHAVIOR	CLINICAL FEATURES
Jitteriness (recurrent tremors in extremities)	Occurs in sleeping and active awake infants (most pronounced in crying infants) in the first 3 days of life. Diminishes with passive flexion. Stimulus sensitive. Excessive jitteriness may be associated with hypoxic-ischemic encephalopathy (HIE), hypoglycemia, hypocalcemia, sepsis, and drug withdrawal.
Benign neonatal sleep myoclonus	Occurs in normal infants. Rapid migrating jerks involving the distal extremities occurring only in sleep, resolving with arousal. Can be quite intense, and occur for long periods during sleep, leading to misdiagnosis of status epilepticus. EEG is normal. Occurs in the first few days of life and resolves at 4 months.
Hyperekplexia (startle disease)	Excessive startle, with generalized rigidity, sometimes with tonic spasms with associated apnea, and even secondary hypoxic seizure. Can be triggered by nose tapping. Caused by genetic mutation in the presynaptic glycine receptor gene ( <i>GLRA1</i> ). Increased risk of sudden infant death syndrome.
Cardiac arrhythmia	Often accompanied by cyanosis.
Gastroesophageal reflux (Sandifer's syndrome)	Opisthotonic posturing in association with feeding. Improves with treatment of reflux.
Brainstem release phenomena	Decerebrate or decorticate posturing often occurring in neonates with diffuse HIE, with no EEG correlate.
Other "normal baby movements"	Eye rolling, dysconjugate eye movement, hiccups, sucking, chewing, tongue thrusting.

**TABLE 5.2 Neonatal Seizure Risk Factors**

Low birth weight <1500 grams
Male sex
Advanced maternal age >40 years
Maternal history of gestational diabetes
Evidence of perinatal hypoxia: fetal distress, placental abruption, cord prolapse
Maternal intrapartum fever or infection
Maternal substance abuse
Moderate-to-severe EEG background abnormalities: excessive discontinuity, burst suppression, very low voltage or isoelectric

Source: From Refs. (1,2).

## ETIOLOGIES

A list of the etiologies of neonatal seizures and neonatal epilepsy syndromes are provided in Tables 5.4 and 5.5. The most common causes include hypoxic-ischemic encephalopathy (HIE) (40%–60%), intracranial hemorrhage (7%–18%), ischemic stroke (6%–17%), congenital brain malformations (3%–17%), and CNS infections (2%–14%) (1). Although relatively uncommon, metabolic disturbances (3%–5%) such as hypoglycemia, hypocalcemia, hypomagnesaemia, and hyper/hyponatremia should be assessed for, as these are easily treated, and in some cases may result in secondary brain injury if left untreated (1). Withdrawal seizures from maternal drug use may also be a precipitant, including prolonged exposure to cocaine, alcohol, narcotics, and tricyclic antidepressants. Inborn errors of metabolism are an overall relatively rare cause of neonatal seizures, but should be suspected in patients without one of the more common

etiologies, especially in those patients refractory to standard therapies. There are several vitamin-responsive epilepsies (pyridoxine, folinic acid, biotin, and pyridoxal-5-phosphate) encountered in this age group that are important to recognize as supplementation often results in improved seizure control. Glucose transporter deficiency (CSF/serum glucose ratio  $\leq 0.45$ ) is also crucial to diagnose as these patients have a relative shortage of CNS glucose to use as fuel. This typically results in epileptic encephalopathy with severe cognitive impairment, unless placed on the ketogenic diet, which has been very successful in treating both seizures and improving cognitive outcomes.

## DIAGNOSTIC EVALUATION

In a neonate with suspected seizures, the first step is assessing for any life-threatening emergencies that would need to be addressed. This includes assessment for readily treatable metabolic causes (glucose, calcium, magnesium, sodium, and hypoxia), as well as assessment for infectious etiologies with blood work and lumbar puncture. In patients where seizure suspicion is high, performing some form of urgent neuroimaging (head ultrasound will suffice in most cases) to assess for neurosurgical emergencies is strongly recommended. The next step in the diagnostic evaluation is confirming that seizures are actually present with EEG. The American Clinical Neurophysiology Society (ACNS) has published high-risk clinical scenarios for which continuous EEG monitoring for seizure detection should be considered (Table 5.6) (3).

As 80% to 85% of patients have HIE, ICH, cerebral brain malformation, or CNS infection, etiology can be determined



TABLE 5.3 Maturation of Normal Neonatal EEG Background

AGE (CA)	CONTINUITY/SLEEP	INTERBURST INTERVAL AMPLITUDE	INTERBURST INTERVAL DURATION	BURST SYNCHRONY	OTHER FEATURES
24–29 weeks	No sustained continuity, TD	<25 mV	6–30 sec	100%	Monorhythmic delta in the occipital, temporal, and central regions
	EEG unchanged in AW/AS				Delta brushes are present
30–34 weeks	AW and AS EEG the same, with longer periods of continuity; TD during QS	<25 mV	5–20 sec	70%–80%	Monorhythmic delta in the occipital, temporal, and central regions  Rhythmic temporal theta bursts  Delta brush seen more in AS than QS  Frontal sharp transients(enconches frontales) first appear at 34 weeks
35–36 weeks	Continuous (AM) in AW/AS, TA in QS	25–50 mV	4–10 sec	90%	Abundant delta brushes more in QS than AS
37–40 weeks	AM in AW/AS, TA and CSWS in QS	50–75 mV	2–4 sec	Nearly 100%	
41–44 weeks	AM in AW/AS, TA and CSWS in QS	75–100 mV	2–4 sec	100%	Delta brush only in QS
45–46 weeks	CSWS with sleep spindles, REM	Continuous	Continuous	100%	Delta brush and frontal sharp transients disappear

Reactivity appears in the neonatal EEG around 30 to 34 weeks, and is absent prior to this time.

Trace discontinu (TD): Bursts of high-voltage (50–300  $\mu$ V pp) activity interrupted by low-voltage interburst periods <25 $\mu$ V (4)

Trace alternant (TA): Alternating activity of high voltage (50–150  $\mu$ V pp) lasting 4 to 10 seconds, followed by lower voltage (25–50  $\mu$ V pp) theta and delta frequencies (4)

Activité moyenne (AM): continuous low to medium voltage (25–50 $\mu$ V pp) predominantly delta and theta with overriding beta (4)

Quiet Sleep (QS): regular breathing pattern, no body movement (4)

Active sleep (AS): irregular breathing pattern; myoclonus of the face, eyes, and body (becomes REM sleep at 45–46 weeks) (4)

Awake (AW): irregular respirations and spontaneous limb movements (4)

in most patients with neuroimaging and lumbar puncture (1). Once seizures have been controlled and the patient stabilized, MRI is the neuroimaging method of choice. If MRI is normal and there is no evidence of infection or acute metabolic disturbance, performing evaluation for inborn errors of metabolism and genetic disorders is warranted. Magnetic resonance spectroscopy (MRS) may be helpful in diagnosing mitochondrial and creatine disorders. Summary of the diagnostic work up is provided in Table 5.7.

Neonatal seizures have been classified into the following categories: clinical only, electroclinical, and electrographic only (4). A clinical-only seizure has been defined as a sudden paroxysm of abnormal clinical changes that do not correlate with a simultaneous EEG seizure (4). An electroclinical seizure has definite clinical signs with a simultaneous EEG seizure (4). Finally, an electrographic seizure refers to the presence of definitive EEG seizure (a sudden abnormal EEG event defined by a repetitive and evolving pattern with a

minimum 2  $\mu$ V voltage and duration of at least 10 seconds) that does not provoke a visible clinical response (4). The term evolution implies unequivocal change in frequency, voltage, morphology, or location (4). Clinical diagnosis of seizures provides a gross underrepresentation, as more recent continuous EEG monitoring studies have reported only 9% of all neonatal seizures having clinical correlation (5). Furthermore, even in patients with clear electroclinical seizures, administration of IV antiepileptic drugs often results in electroclinical dissociation (58%), whereby the clinical seizures stop, but the electrographic seizures persist (6). As such, continuous EEG monitoring is essential in the management of these cases.

Conventional EEG is the gold standard for detection for seizures in neonates. Routine EEG, lasting 30 to 60 minutes, although helpful in providing background assessment, is not adequate to fully assess for the presence of seizures. As such, continuous EEG monitoring is required. As most seizures occur within the first 24 hours of recording, it has been

**TABLE 5.4 Etiologies of Neonatal Seizures**

Hypoxic-ischemic encephalopathy
Intracranial hemorrhage
Ischemic stroke
Venous sinus thrombosis
Congenital brain malformation
Meningitis/sepsis
Congenital TORCH infections
Hypoglycemia
Hypocalcemia
Hypomagnesemia
Hypo/hypernatremia
Maternal drug withdrawal
Inborn errors of metabolism
– Pyridoxine-dependent epilepsy*
– Folinic acid-responsive*
– Pyridoxal-5-phosphate dependent epilepsy*
– Biotin deficiency*
– Glucose transporter defect*
– Creatine deficiency*
– Amino acidemias
– Organic acidemias
– Mitochondrial disorders
– Nonketotic hyperglycinemia
– Sulfite oxidase deficiency
– Peroxisomal disorders
– Congenital disorders of glycosylation*
– Creatine disorders
– Smith-Lemli-Opitz
Kernicterus
Epilepsy syndromes

\*Potentially treatable disorders with appropriate supplementation or dietary changes

suggested that monitoring be performed over this same time frame (3). In neonates receiving hypothermia, seizure onset may be delayed until rewarming, thus monitoring through hypothermia until the patient has been warmed reasonably (3). Once seizures have been detected, monitoring should continue until the neonate is at least 24 hours seizure free (3).

## TREATMENT OF NEONATAL SEIZURES

As there is a growing body of literature to suggest that the presence of neonatal seizures can contribute negatively to neurodevelopmental outcome, clinicians have become more aggressive in their diagnosis and management. Unfortunately, there is a paucity of data in this regard. Data from randomized controlled studies are very limited, and have shown underwhelming effectiveness for the agents routinely used today (phenobarbital and phenytoin, effective in approximately 50% of cases) (7). Despite this, these medications remain our “drugs of choice” mainly because of our comfort level with their use, and lack of any other well-studied options. Table 5.8 provides the dosing for medications frequently used to treat neonatal seizures, as well as some emerging therapies to be considered when seizures do not respond to the traditional therapies (7,8). In neonates with refractory seizure, vitamin supplementation with pyridoxine, pyridoxal 5-phosphate, and folinic acid should be strongly considered (Table 5.8) (7–8). Future studies evaluating the efficacy of new antiepileptic drugs, as well as addressing the even bigger question as to whether the treatment of neonatal seizures impacts outcome are desperately needed.

**TABLE 5.5 Neonatal Epilepsy Syndromes**

EPILEPSY SYNDROME	CLINICAL FEATURES
Benign neonatal seizures (fifth-day fits)	Diagnosis of exclusion, etiology unknown. Occurs in normal infants, typically occurring day 4 to 6, followed by resolution. Seizures typically clonic. Interictal EEG often normal, although may have multifocal spikes and discontinuity. Outcome is typically good.
Benign familial neonatal seizures	Secondary to mutation in the voltage-gated potassium channel gene ( <i>KCNT1</i> ). Autosomal dominant, often with strong family history. Seizures typically occur in the first week, and usually remit in the first 6 months with good outcome, although a small percentage will have epilepsy later in life. A more severe phenotype associated with malignant epilepsy and neurodevelopmental disabilities has also recently been described with mutations in this gene.
Early myoclonic encephalopathy / Early infantile epileptic encephalopathy	Onset within the first month of life. Seizures manifest as focal myoclonus, generalized myoclonus, focal seizures, and tonic spasms. EEG classically reveals burst-suppression pattern. Often associated with inborn errors of metabolism or genetic mutations ( <i>ARX</i> , <i>CDKL5</i> , <i>STXBP1</i> , <i>SLC25A22</i> , <i>SPTAN1</i> , <i>PLCβ1</i> , <i>MAGI2</i> , <i>PNKP</i> , <i>SCN1A</i> , <i>PCDH19</i> , and <i>PNPO</i> ). All infants severely neurologically impaired.
Malignant migrating epilepsy of early infancy	Severe recurrent seizures commonly starting within a few weeks of birth. The seizures are resistant to therapy. Affected individuals have severe neurocognitive deficits and developmental delays. Seizures are focal and appear in multiple locations migrating from one region to another. Status epilepticus is common. Mutations in the <i>KCNT1</i> gene have been found in several individuals, although not all.

Source: From Ref. (1). Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med.* 2013;18(4):185–191.

**TABLE 5.6 ACNS Guidelines: High-Risk Clinical Scenarios for Which Continuous EEG Monitoring for Seizure Detection Should be Considered**

- Acute neonatal encephalopathy
  - Birth asphyxia
  - S/p cardiac arrest
- CNS Infection
- CNS Trauma
- IEM
- Perinatal stroke or SVT
- Clinical seizures/ movements suggestive of seizures
  - especially if AEDs have been given
- Spells of unknown etiology
  - Apnea
- Congenital heart disease
  - s/p by-pass
- ECMO
- Genetic syndrome involving brain

\*Recommend all patients be monitored a minimum of 24 hours  
 Source: From Ref. (3). Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. *J Clin Neurophysiol.* 2011;28(6):611–617.

**TABLE 5.7 Diagnostic Evaluation of Neonatal Seizures****MRI/MRS**

Blood: CBC, CRP, glucose, calcium, sodium, magnesium, amino acids, AST/ALT, lactic acid, acyl carnitine profile, ammonia, free and total carnitine, serum glycosylation studies, biotinidase, pipelicolic acid, very-long-chain fatty acids, aminoadipic acid semialdehyde, 7-dehydrocholesterol. Consider TORCH PCRs. If dysmorphic features are present, consider routine karyotype and chromosomal microarray. Consider genetic infantile epilepsy panel.

Urine: urine organic acids, urine sulfite oxidase/guanidoacetic acid, urinary purines

CSF: cell count, glucose (perform blood to CSF ratio), protein, Gram stain, culture, HSV/CMV PCR, lactic acid, amino acids, neurotransmitters, pyridoxal-5-phosphate, and 5-methyltetrahydrofolate.

Dilated eye examination to assess for evidence of TORCH or genetic conditions.

Consider muscle biopsy

Source: From Ref. (9). Hallberg B, Blennow M. Investigations for neonatal seizures. *Semin Fetal Neonatal Med.* 2013;18(4):196–201.

Neonatal seizures are common and often difficult to diagnose. Many types of nonepileptic spells can mimic seizures and often seizures are only evident electrographically. Continuous EEG monitoring is essential in diagnosing and managing these patients. Neuroimaging will

**TABLE 5.8 Commonly Used Antiepileptics for Neonatal Seizures**

AED	LOADING DOSE	MAINTENANCE
Phenobarbital	20–40 mg/kg IV	5 mg/kg
Fospheytoin	20 mg/kg IV	5 mg/kg
Midazolom	0.05–0.2 mg/kg IV	0.15–0.5 mg/kg/hr
<b>Refractory seizures</b>		
Levetiracetam	30–40 mg/kg IV	20–60 mg/kg IV
Topiramate	None	1–25 mg/kg PO
Lidocaine	2 mg/kg IV	5–7 mg/kg/hr IV
Pyridoxine	100–500 mg IV	5–30 mg/kg PO
Folinic acid	3 mg/kg PO	3 mg/kg PO
Pyridoxal-phosphate	30 mg/kg PO	30 mg/kg PO

Source: From Refs. (7,8).

often reveal the etiology of seizures. Though rare, there are some treatable causes for neonatal seizures, and they should always be sought, as treatment can modify the disease course. Treatment of the seizures themselves usually involves using routine AEDs, such as phenytoin and phenobarbital.

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# Epidemiology

*Sanjeev V. Kothare*

## 6

### CHAPTER

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The epidemiology of epilepsies across ages is described, with specific emphasis on incidence and prevalence for age, gender, type of seizures and epilepsy syndromes, etiology, efficacy of surgery and effect of medications and their withdrawal during remission, recurrent risks, prognosis, and mortality. The epidemiology of status epilepticus (SE) is also discussed. A short description on the epidemiology of sudden unexpected death in epilepsy (SUDEP) has also been provided. Appropriate definitions of epidemiological terms have been discussed. A list of appropriate references for additional reading is provided at the end.

#### DEFINITIONS

Epidemiology is the study of the distribution and determinants of a disease in human populations; the study of the dynamics of a medical condition in the community. It can be classified into three aspects: descriptive, analytical, and experimental (1).

Descriptive epidemiology concerns the incidence and prevalence, and the natural history (prognosis and mortality) of a condition. It may be thought of as observational, with no designed control group (2). Analytical epidemiology compares those with a disease or risk factor with those without, for example, in cross-sectional, cohort, and case-control studies. Experimental epidemiology includes studies under conditions that allow an investigator to control relevant factors. The epidemiology of epilepsy is largely based on descriptive and analytical studies (3).

The incidence rate of a condition is the number of persons who become diseased during a defined period divided by the total person-time at risk during that period. It is generally expressed as the number of cases per 100,000 people in the population per year. The point prevalence rate is the number of diseased persons in a defined population at one point in time, divided by the number of persons in that population and time.

Despite epilepsy being among the most common serious neurological conditions, the reported incidence and prevalence figures vary widely. This may be due to differences in case ascertainment, differences in age groups studied, and differences in location of the study (4).

Before 1960, most studies of epilepsy were based on patients seen in tertiary care centers. These tended to show that epilepsy was a chronic, progressive and incurable disease. Underreporting, inaccurate assessment, and diagnosis of seizures, and inappropriate and inaccurate coding are important examples of ascertainment bias. Appropriate inclusion criteria such as inclusion of neonatal seizure, febrile seizures, and acute symptomatic seizures may further confound this bias.

The incidence of epilepsy is higher in children and the elderly (5,6). About 50% of cases of epilepsy start in the two extremes of life, with half of those being under 1 year.

In general, higher incidences of epilepsy have been reported from developing countries, especially Latin American, African, and many Asian countries (7,8). This may be related to a higher prevalence of parasitic infections, intracranial infections, perinatal brain damage, head trauma, and hereditary factors. Racial differences have also been found, including higher incidence and prevalence among African Americans in the United States.

#### INCIDENCE AND PREVALENCE

The overall incidence of epilepsy, excluding febrile seizures and single seizures, is generally estimated to be about 50 cases per 100,000 persons per year (range 40–70) in developed countries and 100–190 per 100,000 cases per year in developing countries (4). The cumulative incidence of epilepsy (proportion of a fixed population that develops epilepsy in a certain time) is between 2% and 5%, with 1 out of 15 people experiencing an unprovoked seizure at some stage.

The prevalence of epilepsy is usually estimated to be between 4–7 and 7–30 cases per 1,000 persons in developing

countries, excluding febrile seizures, single seizures, and inactive seizures. The lifetime prevalence of developing seizures is between 2% and 5%. Over one-third enter long-term remission and subsequent relapse is uncommon (4).

### Gender and Age

Most studies have cited a slightly higher incidence of epilepsy in males than in females. There is a bimodal age distribution of the incidence of epilepsy, with the highest incidence being reported at 168.5 per 100,000 person-years between ages 75 and 84 years, 110 for age over 65 years, and 130 for infants (1). In contrast, the prevalence of epilepsy increases with age, with the highest prevalence between 10 and 15 cases per 1000 persons above 75 years of age. The prevalence may be lower in the developing countries because of lower life expectancy and quality of care available (9).

### Classification

#### *Seizure Type*

The National General Practice Study of Epilepsy (NGPSE), a prospective population-based cohort of 564 subjects with various seizure types, found that 11% were classified as having complex partial seizures, 3% with simple partial seizures, 27% with secondarily generalized seizures, 35% with primarily generalized tonic-clonic seizures, and less than 1% each with generalized absences and myoclonus. Fourteen percent were mixed (partial and generalized), and 9% were unclassified (1). Generalized seizures are more common in children, while partial seizures are twice as common in adults over 24 years. Similar figures are also seen for the prevalence rates. Misdiagnosing partial from generalized seizures may be an issue in developing countries because of lack of easy access to EEG (8).

#### *Epilepsy Syndrome*

Localization-related epilepsies are the most frequent form of epilepsy in most studies, with 47% having localization-related epilepsy and 34% having generalized epilepsy (9). Between 15% and 20% of epilepsies lack clear focal versus generalized features. In general, the syndrome classification is better suited for classifying childhood-onset epilepsy. In one study from Iceland, incidence rates for various epilepsy syndromes were calculated as follows: nearly 1 per 100,000 for juvenile myoclonic epilepsy and childhood absence epilepsy, nearly 3 per 100,000 for benign rolandic epilepsy, 0.007 per 100,000 for West syndrome, and less than 0.5 per 100,000 for benign occipital lobe epilepsy, benign familial infantile convulsions, and Landau-Kleffner syndrome (4).

### ETIOLOGY

A recent community-based magnetic resonance imaging (MRI) study found that in newly diagnosed patients, a

relevant putative etiology could be found in 70% of those with partial-onset seizures and 30% of those with generalized seizures. Improvement in better imaging and genetic/metabolic testing will lead to an improved yield for finding an etiology in the future.

### PROGNOSIS

#### Recurrence After Single Seizure

The overall risk of seizure recurrence is 40% in prospective studies and 52% in retrospective studies. Two-thirds of the cases have their recurrence within a year, and about 80% within 3 years. The overall risk of seizure recurrence decreases with time.

#### Recurrence After Second Seizure

After the second seizure in a patient, the cumulative risk of a further seizure recurrence is 32% at 3 months, 41% at 6 months, 57% at 1 year, and 74% at 4 years. The risk is reduced significantly if there were no recurrence beyond 4 years.

#### Short- to Long-Term Prognosis

The short-/medium-term prognosis is favorable, with 60% to 70% of patients achieving remission. About 60% to 70% of cases achieve remission in the long term with or without treatment. Remission is more likely with childhood epilepsies.

#### Prognostic Factors

Remote symptomatic epilepsy, presence of a neurologic birth defect, and learning disability have consistently been shown to be associated with a poor prognosis (4). The number of seizures in the first 6 months after seizure onset is a strong determinant of the probability of subsequent remission. More than 10 seizures in 6 months after seizure onset are associated with a lower chance of going into remission on or off treatment. Similarly, seizure freedom within 3 months of initiating therapy seems to be a strong predictor of subsequent remission. Seizure clusters are a poor prognostic factor.

Among patients who have not received any antiepileptic drug (AED), 47% become seizure free on their first AED, and an additional 14% on a second or third drug (10). In addition, only 3% are controlled with a combination of two AEDs. Eleven percent of those who did not achieve seizure control on using the first appropriate AED respond to the second drug. Approximately 4% to 5% of patients with refractory epilepsy will achieve seizure control eventually on a combination of multiple AEDs. There is no significant difference in the seizure-free rates between patients taking an established AED and those taking a newer AED. Primary generalized epilepsy has the best prognosis for seizure



control and hippocampal sclerosis the worst for seizure control on AEDs. Immediate treatment with AEDs delays the early recurrence of seizures but does not affect the medium- or long-term prognosis.

### Prognosis Following AED Withdrawal

After two or more years of seizure freedom, the chance of recurrence of seizures is 41% for those in whom AEDs have been discontinued. When AEDs are continued, the recurrence rate is 22% (4). On reinstating the AED for seizure recurrence, the chance of achieving seizure freedom again is 80%. Thus, the long-term prognosis for both groups is similar.

### Prognosis Following Epilepsy Surgery

In appropriately selected patients with refractory partial epilepsy, surgery is 4 times more likely to render patients seizure free (42%) as compared to medical treatment alone (8%).

## MORTALITY

People with epilepsy have a two- to threefold increased risk of premature death compared with the general population. This is more so in patients with neurological deficits and symptomatic seizures, while the risk in idiopathic generalized epilepsy is the same as in the general population.

### Mortality in Epilepsy

Standardized mortality rate (SMR) is defined as the ratio of observed deaths in a cohort divided by the number of expected deaths in the age-/sex-specific population. The SMR in patients with a newly diagnosed, unprovoked seizure ranges from 2.5 to 4. In young children and those with remote symptomatic epilepsy, the SMR is higher (1). Reported SMRs for epilepsy from developed countries range from 1.6 to 4.1, more so in males than in females for unclear reasons and in children due to the underlying etiology of the epilepsy syndrome.

### Cause of Death

The cause of death can be divided into epilepsy-related and non-epilepsy-related. Common non-epilepsy-related causes include pneumonia, cerebrovascular disease, malignancy, and heart disease. Deaths directly related to epilepsy include sudden unexpected death in epilepsy (SUDEP), SE, and accidents, as a consequence of the seizures including drowning, drug toxicity, and suicide (4).

### Sudden Unexpected Death in Epilepsy

The incidence of SUDEP is 1 in 1000 persons with epilepsy (in the general population it is 1 in 40,000). In patients with

refractory epilepsy, it is 1 in 100 to 200, but is four times less likely in children. Identified risk factors for SUDEP include younger age of onset of epilepsy, higher seizure frequency, refractory epilepsy, longer duration of epilepsy, occurrence of tonic-clonic seizures (especially at night during sleep), use of two or more AEDs, noncompliance with AEDs, substance abuse, mental retardation, neurological deficits, and remote symptomatic etiology for the epilepsy. SUDEP is discussed in more detail elsewhere in this text.

## STATUS EPILEPTICUS

The epidemiology of SE has a bimodal distribution with peaks in children aged less than a year and the elderly (11–14). Most SE cases have an acute symptomatic etiology. The overall incidence rates for SE ranges from 10 to 41 per 100,000 cases per year (median 20). The incidence is higher in children at 10 to 38 per 100,000 cases per year, more so in ages less than 1 year (50 per 100,000 cases per year). Similarly, the cumulative incidence of developing SE in patients above 65 years is significantly higher at 86 per 100,000. In patients older than 75 years, it is even more at about 400 per 100,000 cases (14). The large variability in the incidence of SE may be due to ascertainment bias, including cases of convulsive versus nonconvulsive SE and prolonged febrile seizures. Gender may also affect incidence. Males are twice more likely to develop SE than females.

Recurrence of SE occurs in less than 20% cases, with the greatest risk of recurrence in the first 2 years after the first episode. The short-term mortality ranges between 7.6% and 22%, while the long-term mortality is around 43%. Age and underlying etiology are the major determinants of mortality. An acute symptomatic etiology is the most common cause precipitating SE. The hospital mortality following SE in childhood is around 3% (range 2.7%–5.2%). Continuous EEG monitoring and early aggressive treatment, especially with adequate doses of benzodiazepines, improves outcomes.

Epilepsy is a common disorder. The prevalence and incidence of epilepsy depends on the population studied. Prospective studies of incidence and prevalence in different settings with standardized protocols (diagnostic accuracy, full case ascertainment, and follow-up) should be strongly encouraged. This will help establish the magnitude of the effect that geographic, genetic, etiology, age, and gender-related variables have on the incidence and prevalence of epilepsy. Similarly, the effect of AEDs must also be investigated. A detailed and complete epidemiologic understanding of epilepsy is essential both from a clinical and public health perspective.

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# Etiology

*Amit Verma*

## 7

### C H A P T E R

Determining the etiology of epilepsy is an extremely important part of managing a patient's seizures. A common question most patients have when they see a specialist is what caused their seizure. Several pieces of demographic information including age, comorbid conditions, and geographical location can help in suggesting an etiology but oftentimes it is the combination of these with imaging that eventually establishes the cause of a patient's seizures. It is extremely important to establish the etiology because that can lead to a more defined treatment protocol for a particular patient and can help establish the prognosis for long-term treatment. In general terms, genetic and developmental etiologies are common in the pediatric age group and etiologies such as traumatic brain injury (TBI), central nervous system (CNS) infections, brain tumors, and cerebrovascular disease are more common in older individuals. With the advances in neuroimaging, it has become possible to identify lesions in patients that were otherwise not visible. However, despite these advances, it is still not possible to determine the etiology in a majority of patients.

There are several studies that have characterized the incidence and etiologies of epilepsy in specific age groups. In one community-based epidemiological study, 60% of patients with a new diagnosis of epilepsy had partial seizures (1). Cerebrovascular disease was the most common etiology accounting for 11% of cases, followed by neurological deficits from birth injuries, mental retardation, and/or cerebral palsy. Cerebrovascular disease, as expected, was more common in the older population and birth injuries were more common in children. It was also noted that the risk of developing epilepsy was high in the pediatric population, plateauing during adult years, and then increasing again in the elderly. In the British National General Practice Study of Epilepsy, etiologies were also found to vary depending on the age group (2). While vascular disease accounted for seizures in 15% of patients, that specific etiology accounted for seizures in 49% of patients if they were above the age of 60 years. Similarly, tumors accounted for seizures in 6% of

patients overall, but 11% of those patients above the age of 60. These and other etiologies will be discussed in detail in this chapter.

#### RISK FACTORS

Risk factors for developing epilepsy are often considered synonymous with the etiology. It is worth noting however that just because a specific risk factor has been identified in a particular patient, it may still not be the actual cause for the development of seizures and epilepsy. The identified risk factor, such as a nervous system infection or alcohol use, may simply be the precipitating factor causing seizures in a patient with another underlying etiology.

#### ETIOLOGIES

There are many causes of epilepsy in the adult population. Common causes include traumatic brain injury (TBI), cerebrovascular disease, brain tumors, cognitive impairment, dementia and neurodegenerative disorders, alcohol- and drug abuse-related seizures, CNS infections and electrolyte disturbances (3). These etiologies will be discussed in further detail in the following sections.

#### Traumatic Brain Injury

TBI is an extremely common yet potentially preventable cause of epilepsy. It increases the risk of seizures both acutely and remotely, and the highest risk is associated with penetrating brain injuries. There has been increasing interest in TBI as it relates to epilepsy because of war-related injuries. The improvements in overall survival following blast and blunt trauma injuries in the battlefield have resulted in a greater number of veterans who have long-term effects of TBI.

Seizures after a TBI can occur (a) immediately—within the first 24 hours after injury, (b) early—within the first

week after injury, or (c) remotely—more than 1 week after injury (4). The risk increases with severe TBI, which includes depressed skull fractures and intracerebral and subdural hemorrhages. The risk of immediate or early posttraumatic seizures is about 25% in this situation. One study found the relative risk of developing epilepsy was twice as high with mild TBI and seven times higher with severe TBI. It was two times higher after skull fracture (5). The risk of epilepsy was highest acutely but remained increased for more than 10 years after head trauma. Similarly data from the Vietnam Head Injury Study evaluated 1,221 Vietnam War veterans with mostly penetrating head injuries (6). There was a very high prevalence (45%–53%) of posttraumatic epilepsy, and 12.6% of patients reported a very late onset of seizures, more than 14 years after the injury. Even though penetrating TBIs have been clearly associated with the risk of developing epilepsy, there are data to suggest that even mild TBI can be associated with a long-term risk of developing epilepsy. Loss of consciousness during the injury appears to correlate highest with the risk of developing epilepsy.

There are several aspects of the treatment of posttraumatic epilepsy that have received significant attention. One is the research focused on using antiepileptic drugs (AEDs) to prevent the development of epilepsy even before seizures have occurred. Other studies have focused on using AEDs once a seizure has occurred. Phenytoin has been shown to prevent early seizures (in the first 7 days) after moderate-to-severe TBI but was not effective in preventing the development of epilepsy at 1 and 2 years (7). Many other agents have been studied, including valproic acid, phenobarbital, carbamazepine, and magnesium, with similar results showing that they were mostly ineffective in the prevention of developing epilepsy.

### Cerebrovascular Disease

Different types of cerebrovascular diseases can be the responsible etiology for epilepsy, depending on the age group. In premature infants, periventricular hemorrhages can occur that increase the risk of seizures in later life. Birth injuries with ischemic-hypoxic injury will increase the risk of seizures as well. In younger patients, developmental abnormalities such as arteriovenous malformations (AVMs) or cerebral cavernous malformations are common causes of seizures. Occlusive cerebrovascular disease and intracranial hemorrhage are common causes of seizures in older patients.

Occult AVMs can sometimes be seen after a first-time seizure. In a population-based study, the 5-year risk of a first seizure was 8% for an AVM and 4% for cerebral cavernous malformation (8). The presence of an intracranial hemorrhage or neurological deficit raised this risk for AVMs to 23%. In the same study, the 5-year risk of developing epilepsy following the first seizure was 58% for AVMs and 94% for cerebral cavernous malformations. It is important to note that the risk of seizures is with arterial malformations, and the risk is typically low with venous malformations. Even

though the risk of hemorrhage with venous malformations is low, there are sometimes small areas of dysplastic tissue that can be present, which can sometimes cause seizures.

Occlusive cerebrovascular disease or stroke is the most common cause of seizures in adults over the age of 60 (9). Stroke is a common enough cause in older patients that a detailed and thorough cerebrovascular workup is warranted when they present with seizures. It has also been found that the risk of a major stroke following a first-time seizure after the age of 65 is approximately 2 to 3 times the general population. Stroke can be associated with both an increased risk of acute seizures and remote seizures. A history of stroke is associated with a significant increase of the lifetime risk of developing epilepsy (10). Risk factors for stroke such as elevated total cholesterol and left ventricular hypertrophy are also associated with an increased risk of seizures. The incidence of early seizures following stroke has been found to be between 2.4% and 5.4%. The risk of remote seizures has been found to be between 3% and 4.5%. Early postischemic seizures, size of stroke, and cortical signs during the stroke increase the risk for subsequent development of epilepsy. Secondarily generalized seizures are very common in the setting of an acute stroke. Status epilepticus can also be a presenting symptom of stroke. In a status epilepticus study, approximately 50% of adult cases were caused by a stroke (11). Status epilepticus after stroke is associated with higher functional disability, and early-onset status epilepticus after stroke is associated with a higher mortality than late-onset status epilepticus. Several studies have shown that larger infarcts and hemorrhagic transformation are associated with a higher risk of developing seizures.

The treatment of seizures and in the setting of a stroke carries many challenges. Seizures are often considered a contraindication to the use of tissue plasminogen activator (TPA) in the setting of an acute stroke. The use of anticoagulation becomes worrisome because of the risk of bleeding in the setting of a seizure. Many injuries can occur during a seizure, and the increased risk of bleeding may contribute to not only increased morbidity but also possibly mortality. Many of the AEDs can also influence the efficacy of anticoagulants and may require frequent monitoring of prothrombin time (PT) and international normalized ratio (INR).

### Brain Tumors

Seizures are very common in patients with brain tumors and are often the first presenting symptom. The initial workup following the seizure typically includes neuroimaging to rule out the presence of a tumor. Brain tumors are present in approximately 1% of patients who have a seizure. If the seizure has a focal onset or there is a presence of a focal deficit in the postictal state, performing neuroimaging to rule out the presence of a tumor is extremely important. Seizures typically develop in at least 35% to 50% of patients who have brain tumors. The type and location of the tumor relates significantly to the risk of developing epilepsy. The risk of

developing seizures is significantly higher for supratentorial tumors versus infratentorial tumors (22%–68% and 6%, respectively). Tumors that approach the central sulcus are also more likely to cause seizures. The risk of developing seizures is higher with slow-growing brain tumors versus rapidly growing ones. Primary central nervous system (CNS) neoplasms are more likely (50%–75%) to cause seizures than brain metastasis (20%). Certain other types of brain tumors such as dysembryoplastic neuroepithelial tumors (DNETs) are considered to be highly epileptogenic. If brain tumors occur at a younger age, the risk of developing epilepsy is higher.

The most common seizure type associated with brain tumors is focal seizures and secondarily generalized tonic-clonic seizures. The specific semiology is consistent with the location of the tumor. Certain tumors such as hypothalamic hamartomas may be associated with specific seizure types like gelastic seizures. Tumors arising from the medial temporal region may be associated with olfactory auras, and their semiology is consistent with temporal lobe epilepsy.

The treatment of seizures associated with brain tumors is related to the treatment of the brain tumor. Complete resection of the tumor often results in resolution of the seizures. One specific exception is the removal of meningiomas. Despite removal of these tumors, there is still a high risk of development or persistence of seizures. This is related to the cortical injury that occurs because of the meningiomas.

### Cognitive Impairment

Cognitive impairment is often thought to be a strong risk factor for the development of epilepsy. Often cognitive impairment, especially in the pediatric population, is associated with other injuries such as perinatal hypoxia, metabolic disorders, neuronal migration disorders, and brain malformations. A common pediatric condition that is associated with cognitive impairment is Lennox-Gastaut syndrome (LGS) (12). This syndrome comprises patients with multiple seizure types, cognitive impairment, and EEG findings that show slow spike wave activity. LGS is often diagnosed between the ages of 2 to 8 years, and 80% of these patients will continue to have seizures as adults. In these patients, the cognitive impairment typically worsens with age.

### Dementia and Neurodegenerative Disorders

Dementia due to cerebrovascular disease carries the same risk of developing seizures as those related to the underlying cerebrovascular disease. There has been an increased risk of seizures and development of epilepsy in patients in the later stages of Alzheimer's disease. Patients who were eventually proven to have Alzheimer's disease on autopsy had a 10-fold increased risk of unprovoked seizures. The seizures that occur in the late stages of Alzheimer's disease are often generalized tonic-clonic. Even though there may be temporal lobe atrophy in these patients

on neuroimaging, the seizures are often not of temporal onset. The diagnosis of Alzheimer's disease or a diagnosis of dementia is associated with a six-fold increased risk of unprovoked seizures (13).

### Alcohol and Drug Abuse-Related Seizures

Although the most common description for alcohol-related seizures is in the setting of alcohol withdrawal, seizures associated with alcohol use may occur in the setting of intracranial hemorrhage, subdural hematomas, acute CNS infection, stroke, metabolic disturbance, or TBI. The term alcohol-related seizures is often reserved for seizures that result as a direct consequence of alcohol use, especially alcohol withdrawal. Alcohol withdrawal seizures are most often generalized tonic-clonic, typically occurring between 6 and 36 hours after the last drink and are often multiple. Chronic daily drinking can cause seizures as well. In patients who present with alcohol-related seizures, it is important to obtain a head computed tomography (CT) to rule out acute injury. Patients who present to emergency departments often do not have any accompanying relatives or friends and can have subdural hematomas or other trauma-related findings (14).

It is important to consider a genetic generalized epilepsy in a patient presenting with an alcohol-related seizure. Alcohol use can often precipitate seizures in patients with juvenile myoclonic epilepsy. In these patients, the first seizure typically occurs in the setting of sleep deprivation and alcohol use. A history of myoclonus and generalized spike-wave discharges recorded on EEG can confirm the diagnosis.

Several recreational and prescription medications have been associated with an increased risk of seizures. Prescription stimulant medications such as dextroamphetamine, methamphetamine, methylphenidate, and pseudoephedrine and recreational drugs such as cocaine and ecstasy are commonly implicated in causing seizures. The risk with prescription stimulant medications that are used to increase alertness in a variety of neurological disorders is often considered very low and seizures mostly occur in the setting of overdose. The risk of seizures in cocaine-intoxicated patients can be up to 9%, and it appears that the risk is higher after smoking crack than after snorting cocaine. Overdosage with ecstasy can cause seizures, coma, and death. Opioids such as heroin rarely cause seizures, and if a patient presents with seizures after heroin use, other etiologies should be considered. Phencyclidine or Angel dust overdose can also cause seizures, status epilepticus, and myoclonus.

Marijuana has recently gained notoriety as a legal recreational drug in some states. With its increasing availability, renewed attention has been focused on its use in patients with epilepsy. In animal studies, cannabidiol has been found to be consistently anticonvulsant. Human data are currently lacking, but studies are underway to assess its utility in various types of epilepsies.



## Central Nervous System Infections

There are a variety of reasons why CNS infections can increase the risk for seizures. Increased intracranial pressure, inflammation, and subsequent occlusion of blood vessels, inflammation of the cortical region and mass effect can cause seizures. Viral, bacterial, fungal, and parasitic infections can result in seizures.

A variety of viruses can cause inflammation of the brain. West Nile, Japanese, Eastern equine, and herpes simplex type I (HSV-1) encephalitis are commonly associated with seizures. HSV-1 encephalitis often affects the perisylvian region with hemorrhages in the temporal region. EEGs in these patients often demonstrate periodic discharges in the temporal region. With encephalitis related to other viruses, the EEG often shows either focal or generalized periodic discharges.

Bacterial infections that are associated with seizures include *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and others. Seizures can occur in up to 40% of patients acutely, and the seizures are often generalized tonic-clonic. Brain abscesses can result from emboli from a distant source such as an infected heart valve or as a result of sepsis. Most abscesses occur at the cortical-subcortical junction and frequently cause seizures. CNS tuberculosis is a common cause of seizures in developing countries. Patients who have CNS tuberculosis often have cranial nerve involvement and are either immunocompromised or from developing countries.

The most common parasitic infection that is associated with seizures is neurocysticercosis. The responsible parasite is *Taenia solium*. It is a very common cause of seizures in developing countries, accounting for up to 30% of epilepsy cases. Seizures can occur at any stage of the cycle of the parasite. Calcified cysticerci are associated with astrocytic gliosis, which is thought to be the etiology of the seizures. Diagnosis is made by neuroimaging and cerebrospinal fluid (CSF) serology. Treatment of neurocysticercosis can result in reduced risk of subsequent seizures.

## Electrolyte Disturbances

Seizures secondary to electrolyte disturbances are common. Common electrolyte disorders that can result in seizures include hyponatremia, hypomagnesemia, uremia, and hepatic failure. Hyponatremia and hypomagnesemia are possibly the most well characterized (15).

Hyponatremia may have different etiologies. Severe hyponatremia defined as serum sodium levels less than 120 mEq per liter can result in neurological symptoms especially if it occurs acutely. Patient may develop cerebral edema and seizures, and in severe cases this may lead to death. Hyponatremia is sometimes also seen with AED therapy, especially carbamazepine, oxcarbazepine, and eslicarbazepine acetate. The risk of clinically significant hyponatremia, which

is defined as less than 125 mEq per liter, is approximately 7% to 8% with carbamazepine and oxcarbazepine and approximately 1.5% with eslicarbazepine acetate. Seizures have also been reported with uremia and less frequently with other metabolic disturbances.

Seizures can have many different etiologies. Patients with epilepsy always wonder why they have seizures. Searching for the etiology of seizures is an important part of the evaluation of every patient with epilepsy. Different etiologies are more commonly seen in different age groups, with birth-related injuries being common in young children, while TBI and cerebrovascular disease are much more common in older individuals. Despite a thorough workup, the etiology of the seizure may remain elusive.

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# Differential Diagnosis

*Pradeep Sahota*

## 8

### C H A P T E R

While the range of treatment options for managing seizures has improved significantly, newly diagnosed epilepsy continues to evoke concern in the mind of the patient as well as the family due to significant psychosocial, vocational, functional, and other implications. Given these concerns, it is important to make an accurate diagnosis of a seizure disorder and subsequently initiate the most appropriate treatment. To do so, seizure mimics must be ruled out. An improved understanding of both epileptic and nonepileptic disease processes has increased the possible differential diagnosis of spells (1–4). In addition, the development of better diagnostic methods (video EEG or vEEG monitoring, neuroimaging techniques) has expanded the ability to detect a range of seizure mimickers. Despite all these advances, the history obtained from the patient and observer remains vital to the diagnosis.

A variety of medical, neurological, and psychiatric conditions may mimic seizures and should be considered in the differential diagnosis of seizures. This chapter will focus on differential diagnosis of seizures.

#### CLINICAL PRESENTATION OF SEIZURES

A seizure may be defined as an event consisting of a paroxysmal, abnormal, excessive, disorderly neuronal discharge that may be accompanied by a variety of different clinical manifestations, depending on the site of origin, extent of neuronal involvement, and pattern of spread (5). Generalized seizures involve both hemispheres at the outset, whereas partial seizures start in a focal area. Hence, depending on the site of involvement and spread, almost any neurologic symptom or set of symptoms can be a manifestation of a seizure. These symptoms may include motor, sensory (somatosensory or special sensory), autonomic, and psychic manifestations, in addition to the loss or impairment of consciousness.

While the list of symptoms is broad, there are features that can cue clinicians toward the diagnosis of a seizure disorder. These include: history of prodromal symptoms,

onset of symptoms, evolution of the event, and duration of the event (seconds to minutes, usually no more than a couple of minutes) and postevent features including focal weakness, confusion, and findings of tongue biting, and bladder-bowel incontinence. The stereotypical nature of these clinical manifestations is a salient feature of seizures. In addition, age of onset, knowledge of the precipitating factors, and relieving factors as well as the circumstances in which the events occur may be important.

A number of medical, neurological, and psychiatric disorders can have clinical presentations resembling those seen with seizures. Examples of medical disorders include syncope, cardiac disease, hypoglycemia, dizziness, and vertigo. Neurological disorders including transient ischemic attack (TIA), transient global amnesia, complicated migraine, movement disorders, and sleep disorders may also mimic seizures. Psychiatric disorders, including psychogenic nonepileptic seizures (PNES), anxiety or panic attacks, and certain physiological events such as hypnic myoclonus, may at times be also mistaken for seizures.

Given that the clinical presentations of seizures can vary widely based on the presence of motor, sensory and autonomic features, and impairment of consciousness, the differential diagnosis is best considered for each type of presentation. This approach is arbitrary but helps to differentiate seizures from other nonepileptic events based on the initial presentation with the caveat that some seizures may have a combination of motor, sensory, and other features.

#### Presentation With Motor Features

Both partial and generalized seizures can present with motor features. The movements may involve an extremity or all four extremities. They may be rhythmic and repetitive or organized and evolving. The movements can be tonic, clonic, myoclonic or semi-purposeful, versive eye movements with deviation of eyes to one side, or automatisms in the form of blinking, lip smacking, chewing, wringing

**TABLE 8.1 Differential Diagnosis of Seizures Presenting With Motor Features**


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Sleep disorders – night terrors, sleep walking, narcolepsy with/without cataplexy, REM behavior disorder
Movement disorders – tics, paroxysmal nocturnal dystonia, nonepileptic myoclonus
Transient ischemic attack/stroke
Hyperekplexia
Catatonia
Psychogenic events

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or fumbling movements of the hands and extremities. The movements can evolve – starting with a tonic component and progressing to clonic activity. There may be vocalization or speech arrest. Usually, these findings are often stereotypical. They last seconds to minutes and rarely longer. Epilepsia partialis continua (EPC) is a unique condition where the movements can last up to days. The events may be preceded by aura (simple partial component) consisting of abnormal or unusual smell, taste, abdominal sensation. They may be followed by weakness of the involved extremity (Todd's paralysis). Other clinical conditions that present with motor features include sleep disorders, movement disorders, TIA, hyperekplexia, and catatonia (Table 8.1).

### *Sleep Disorders*

While seizures may occur at night, occasionally other sleep disorders may present a diagnostic challenge and may need to be distinguished from seizures. These include night terrors, sleep walking, rapid eye movement (REM) behavior disorder (RBD), and narcolepsy with/without cataplexy.

*Night terrors* are usually seen in children and consist of sudden awakening from sleep with loud crying. The child appears to be in a state of fear and shock and is confused and almost inconsolable. He or she is unable to follow the commands of the parents or caregiver. The event lasts several minutes before the child is able to fall back to sleep. It can be distinguished from nightmares, as there is no dream phenomena associated with it. These events occur in stage III sleep.

*Sleepwalking* (like night terrors) is also frequently seen in children and tends to resolve by the late teenage years. The episodes of sleepwalking consist of the patient getting out of bed and walking around the house or sometimes even opening the door and walking outside. The event may last several minutes. Again, there are no accompanying dream phenomena and the patient usually does not have any recollection of the episode later on. Sleepwalking also occurs during stage III sleep.

*RBD* is characterized by vivid dreams with dream enactment (6). Depending upon the dream content, the accompanying behaviors may involve vocalizations, organized

movements, or dangerous violent manifestations. In comparison with night terrors and sleepwalking, these episodes occur during REM sleep. An overnight polysomnogram (PSG) may reveal significantly increased muscle tone during REM sleep and dream enactment motor behavior, should the patient happen to have one of these episodes during the night of the recording. The disorder may be idiopathic or may occur in the setting of a variety of synucleonopathies. In fact, the disorder may predate the onset of other recognized symptoms of these degenerative neurological disorders.

*Narcolepsy* is characterized by excessive daytime sleepiness and sleep attacks. Sleep attacks represent acute onset of sleep, can be brief (microsleep), and may contribute to automatic behavior. Cataplexy is the acute, brief, partial, or complete loss of muscle tone usually precipitated by emotions. The acute paroxysmal nature of the presentation of narcolepsy/cataplexy may be confused with seizures as the patient has sudden loss of tone and often falls down during the cataplexy events. During these events the patient is conscious and aware unless sleep follows. An overnight PSG followed by multiple sleep latency test (MSLT) is helpful for diagnosing narcolepsy. Low cerebrospinal fluid (CSF) hypocretin level may be diagnostic, but the need for spinal fluid sampling and its limited availability makes this an uncommonly employed test.

### *Movement Disorders*

Most movement disorders are chronic disorders that may be persistent or progressive and are usually easy to distinguish from seizures. However, some movement disorders are episodic or paroxysmal.

*Tics or habit spasms* are spontaneous, purposeless movements with the associated urge to execute the tic and transient relief afterward. Movements include blinking, eye movements, shoulder shrugging, head-nodding, sniffing, or throat clearing, and may occur in isolation or constitute a sequence of movements without any accompanying neurological deficits.

*Paroxysmal dyskinesias* consist of dystonic posturing, chorea, athetosis, and hemiballismus that can be unilateral or bilateral and may affect one region of the body or may be generalized. For instance, nocturnal paroxysmal dystonia is characterized by bursts of generalized choreo-athetotic, ballistic, and dystonic movements occurring during non-REM sleep (7). However, there have been reports of brief episodes of nocturnal paroxysmal dystonia lasting less than a minute in which vEEG monitoring showed evidence of frontal lobe epilepsy (8). Longer-lasting episodes spanning several minutes with no associated EEG abnormalities are thought to be nonepileptic.

*Nonepileptic myoclonus* consists of isolated jerky movement without any accompanying electrographic epileptiform abnormalities. It can arise from several foci in the central nervous system including the spinal cord or brainstem. A common form is hypnic myoclonus, which are isolated myoclonic movements during transition to sleep.

*Hemi-facial spasms* are recurrent lateralized contractions of the facial muscles. They may be idiopathic or caused by vascular compression of the facial nerve. They can also be seen in patients with other conditions such as multiple sclerosis (MS).

### ***Transient Ischemic Attack***

TIAs are characterized by acute onset of weakness, numbness, language difficulty, gait difficulty, or loss of vision. They are acute in onset and consist of loss of motor or other functions rather than abnormal movements that are uncommon. Rarely nonrhythmic involuntary movements of the involved extremity can be seen in carotid artery TIAs. Posterior circulation TIAs may be accompanied by acute vertigo, double vision, blurry vision, dysarthria, and ataxia. TIAs usually last longer than seizures (most events last less than 30 minutes, though by definition can last up to 24 hours). They may occur in patients with known cerebrovascular disease or may be the initial presentation. Hence, it should be noted that TIAs may be the warning signs of future strokes and should be carefully evaluated. Stroke has longer-lasting motor, sensory, language, or other deficits. Acute confusional states have been reported with cases of right middle cerebral artery strokes (9).

### ***Hyperekplexia***

Hyperekplexia represents exaggerated startle response, often noted to start in infancy, that may lead to a fall. This condition needs to be distinguished from startle-induced epileptic seizures (10) that may consist of noise (or other somatosensory or visual stimuli) that may induce asymmetric tonic posturing (11).

### ***Catatonia***

Catatonia is seen in patients with schizophrenia. It consists of tonic posturing with a tendency to tonically maintain the extremity in a given position, sometimes referred to as waxy flexibility. It can be seen in other conditions such as Down syndrome and Prader-Willie syndrome.

## **Presentation With Sensory Features**

Partial seizures may be associated with sensory or special sensory features. These can include abnormal smell, taste, visual imagery (including formed images such as faces, scenes, or unformed lights or colors), feelings of strange familiarity (*déjà vu*), epigastric/abdominal sensations, feelings of dizziness or vertigo, and somatic sensations involving the extremity or extremities. Other clinical conditions that present with sensory features include TIAs (discussed earlier), migraines, hypnagogic hallucinations, paroxysmal painful episodes, and transient paresthesias (Table 8.2).

### ***Migraine***

Classical and complicated migraines may have transient neurological features that mimic seizures. Classic migraine

**TABLE 8.2 Differential Diagnosis of Seizures Presenting With Sensory Features**

Migraine
Hypnagogic hallucinations
Paroxysmal painful episodes
Transient paresthesias

usually consists of a visual aura in the form of a scintillating scotoma that evolves over several minutes. There may be other transient sensory symptoms. While stereotypical in nature, the presence of the visual aura followed by a severe headache with much slower evolution of symptoms taking several minutes distinguishes a migraine headache from a seizure. Confusional migraine may have an additional component of mental status change. Complicated migraines may be accompanied by neurological deficits like lateralized weakness, referred to as a hemiplegic migraine. The weakness can be ipsilateral or contralateral to the side of the headache. The events are also stereotypical in nature, but last much longer (though postictal paralysis following a seizure can last minutes to hours or longer as well), and usually there is a family history of migraines.

### ***Hypnagogic Hallucinations***

These are visual or somatosensory hallucinatory experiences that can be present during transition to sleep (rarely when waking up, referred to as hypnapompic hallucinations). They represent an abnormality of state transition. The patient is usually aware of these events and has insight that they represent hallucinatory experiences. They can occur independently or in association with narcolepsy where they represent dream phenomena associated with sleep-onset REM.

### ***Paroxysmal Painful Episodes***

Pain as an isolated manifestation of seizures (12) has been reported but is uncommon. Sudden, jabbing lateralized facial pain can be seen in patients with trigeminal neuralgia. It may be precipitated by touching the gums or teeth. It is easily distinguished from seizures, though it may respond to antiepileptic medications such as carbamazepine. However, rarely acute-onset, lateralized, and evolving extremity pain has been documented as a manifestation of partial seizures (6,13).

### ***Transient Paresthesias***

Transient numbness, weakness, and paresthesias are known to occur in patients with MS. These symptoms may also present in an episodic fashion. However, they tend to be significantly longer in duration than is typical for seizures.



MS consists of features of motor, sensory, visual, and other neurologic dysfunction. Magnetic resonance imaging (MRI), visual evoked potentials, and CSF studies for myelin basic proteins and oligoclonal bands are helpful in the diagnosis of MS. In addition, patients with MS can present with tonic contractions of their extremities (14). However, typical seizures are rather uncommon in patients with MS.

**Presentation With Impairment of Consciousness**

Both partial and generalized seizures can have impairment of consciousness as one of the component features. In complex partial seizures, impairment of consciousness can be in the form of lack of awareness, decrease in responsiveness, impairment of memory, or complete loss of consciousness with secondary generalization. During a primary generalized seizure, there is usually no memory of the event whatsoever. In absence seizures, there is sudden onset of brief impairment of consciousness or decreased responsiveness, followed by sudden offset without any postevent neurological deficits. Other clinical conditions that present with impairment of consciousness include syncope, drop attacks, transient global amnesia, dizziness and vertigo, anxiety and panic attacks, and psychosis (Table 8.3).

*Syncope*

Syncope is common and is reported to account for approximately 3% of emergency department visits (15). It is caused by the acute loss of consciousness secondary to a sudden decrease in cerebral blood flow due to a variety of etiologies. These include vasovagal syncope, orthostatic syncope, reflex syncope (eg, micturition syncope and cough syncope) (16), and cardiac abnormalities such as arrhythmias, cardiomyopathies, and long QT syndrome. In vasovagal syncope, the patient is usually in an upright posture. Excessive heat, painful or fearful experience (like blood draw) may precipitate syncope. The onset is characterized by dizziness, blurring of vision, pallor, and an impending feeling of passing out. Sometimes, immediate lying down may prevent complete loss of consciousness and is then referred to as presyncope. Sudden change of posture from recumbent to upright position may also cause orthostatic syncope in patients with orthostatic hypotension with associated autonomic neuropathy/autonomic failure and postural orthostatic tachycardia syndrome (POTS). Recumbent posture leads to resolution of the episode.

Syncope caused by cardiac disease does not resolve with assuming a recumbent posture. In these cases, an electrocardiogram (ECG) may reveal a cardiac arrhythmia such as prolonged QT syndrome, Wolff Parkinson White syndrome, etc. Cardiac syncope may also be caused by cardiomyopathies and valvular disorders such as aortic stenosis. There is usually no associated tongue biting or urinary incontinence.

Reflex syncope may occur with micturition (micturition syncope) or coughing (cough syncope). Carotid sinus hypersensitivity can lead to acute loss of consciousness while shaving or during other maneuvers that may put any pressure on the carotid arteries. Acute hypoglycemia may be accompanied by feelings of lightheadedness or impairment of consciousness to loss of consciousness. Such events occur in the setting of a diabetic patient taking insulin without appropriate meal or caloric intake or with accidental overdosing of insulin.

Most syncopal events are not neurologic and can be distinguished from seizures (Table 8.4). EEG, if recorded during the event, may show slowing of the background but does not reveal any epileptiform activity. Tonic-clonic activity or other abnormal movements are not seen in episodes of syncope. However, brief tonic posturing and few isolated clonic or myoclonic movements can be seen. Rarely, syncope when prolonged may be accompanied by convulsive activity and is termed convulsive syncope (17).

*Drop Attacks*

Drop attacks consist of sudden loss of tone leading to falling. These may result from acute vertebro-basilar insufficiency (usually seen in elderly in the setting of cerebrovascular disease) or acute obstruction of CSF outflow, as in colloid cysts of the third ventricle that can be diagnosed by neuroimaging. Cataplexy as noted earlier can also lead to acute loss of muscle tone, usually precipitated by laughter or other emotional triggers and most often occurs in the setting of narcolepsy with excessive somnolence and sleep attacks. Cataplexy without features of narcolepsy is uncommon (eg, Norrie disease).

*Dizziness and Vertigo*

Dizziness and vertigo are seen in patients with vestibular disorders. Dizziness is a somewhat nonspecific symptom, but when seen in association with vertigo suggests involvement of the vestibular system. It consists of a feeling of unsteadiness accompanied by a spinning sensation. Vertigo of peripheral vestibular onset is rather paroxysmal, precipitated by head movement and accompanied by nausea and vomiting. There is accompanying nystagmus that may have a fatiguing nature. Vertigo secondary to central nervous system involvement is less explosive in nature and may be accompanied by nonfatiguing types of nystagmus. The Dix-Hallpike maneuver can help with the diagnosis. Rarely, vertigo can be the presenting features of a seizure that starts in the temporal or insular area. As with other types of seizures, these events are stereotypical in nature and shorter in duration lasting just a couple of minutes.

**TABLE 8.3 Differential Diagnosis of Seizures Presenting With Impairment of Consciousness**

Syncope
Drop attacks
Dizziness/vertigo
Transient global amnesia
Psychiatric disorders



**TABLE 8.4 Characteristics of Seizures Versus Syncope**

CLINICAL PRESENTATION	SYNCOPE	SEIZURES
Posture	Usually upright	Any position
Aura	Lightheaded, dizzy	Seen in partial seizure Olfactory/gustatory/motor/sensory
Onset	Acute, usually slower than seizure onset	Acute
Impairment of consciousness	Yes	With generalized and complex partial seizures
Convulsive or other motor activity	None or brief, isolated tonic or clonic/myoclonic movements	Semi-purposive automatism, lateralized or generalized tonic clonic activity
Duration	Very brief – seconds to minutes, recumbence restores consciousness	1–2 minutes longer if status epilepticus
Tongue biting	Seldom	Seen in generalized seizure
Incontinence	Rare, micturition syncope induced by urination	Seen in generalized seizures
Postevent confusion	Rare	Seen with most seizure types. None in absence seizures
Precipitating factors	Upright posture, pain (blood draw), hypoglycemia, reflex syncope with cough or micturition	Fever (febrile seizures), Photic stimulation, hyperventilation, Sleep deprivation
Relieving factors	Recumbent posture	Individual event usually self-limited; resolution of the fever (febrile seizures in children); medical treatment for recurrent events

### *Transient Global Amnesia*

Transient global amnesia is an acute episode of confusion and memory disturbance that can last for several hours (18). The patient may continue to perform some daily activities during the episode without any memory of the events. Unlike seizures, the episode is longer in duration and simultaneous EEG recording reveals no epileptiform discharges.

### *Anxiety/Panic Disorders*

Acute anxiety and panic attacks consist of acute onset of anxious feelings, palpitations, sweating, dyspnea, generalized trembling, choking, nausea or abdominal stress, depersonalization or derealization, chest pain/discomfort, fear of losing control, and fear of dying (19). Episodes can last minutes to hours. Simultaneous EEG recordings reveal no epileptiform activity. Sometimes, acute anxiety or emotional stress may also be accompanied by hyperventilation and the patient may complain of dizziness, lightheadedness, acro-paresthesias consisting of tingling and numbness in the distal extremities. Physical examination may reveal tachycardia, sweating, and pallor (20).

### *Psychogenic Nonepileptic Seizures*

Many psychiatric conditions can result in PNES. While this topic is covered at length in Chapter 37, a brief discussion of PNES is pertinent here. PNES are seizure-like events of psychogenic origin that can present with a variety of

manifestations that may resemble almost any type of partial or generalized seizures and pose a significant diagnostic challenge.

The incidence of PNES is 3 to 33 in 100,000 persons (21). It is estimated that in patients evaluated at epilepsy centers, PNES account for about 15% to 30% of patients referred for refractory seizures (22). They can be seen in various age groups including children (23) and are more common in women than in men. Clinical features of PNES have been extensively described (24–27). Motor features are predominant and consist of jerky movements that may appear to be tonic, clonic, or myoclonic. The speed and intensity of the movements may vary during the episode. The movements may increase in intensity or may decrease and subsequently increase again in an unpredictable fashion. Certain movement types such as side-to-side head movement, opisthotonic posturing, pelvic thrusting, thrashing movements, crying, and forcible eye closure may be seen. Sometimes the movements may involve the extremities in an alternating fashion. Some of these features can be seen in seizures – especially of frontal onset (28). There may be lack of impairment of consciousness in an episode with features of generalized tonic-clonic activity as the patient is able to respond or converse during the episode. The events may last longer than usual seizures, lasting several minutes. The episodes tend not to respond to usual antiepileptic medications. When prolonged, they may mimic status epilepticus and such patients may receive intravenous abortive anticonvulsant therapies, sometimes with intubation and respiratory support/intervention.

PNES usually occur in the presence of a witness. They tend not to occur during sleep. Tongue biting and urinary or fecal incontinence can occur but are less common than in seizures. The occurrence of the episodes may be suggestive. In the past, provocative tests, such as the administration of intravenous saline, were used to induce typical episodes. However, sometimes, epileptic seizures may also be induced. Hence, there were limitations to the interpretation of induction maneuvers (29). Due to ethical concerns, provocative tests are rarely used now.

Past medical history may reveal history of physical and/or sexual abuse and history of psychological/psychiatric problems in patients with PNES. Maladaptive personality is reported to be common. Conversion or somatization disorders may be mechanisms underlying PNES. Psychiatric evaluation is helpful in the management of PNES. vEEG monitoring during an event may reveal the absence of epileptiform discharges, presence of normal background EEG activity superimposed with myogenic artifact, and absence of postevent EEG abnormalities.

A complicating issue is the presence of PNES in patients who may also have a seizure disorder. PNES have also been reported after surgery for refractory epilepsy (30). The clinical features can be similar to the patient's seizures or can be different.

## DIAGNOSIS

As with all neurological disorders, the first step is to obtain a complete history (from the patient and the observer) including family and personal/social history and perform a physical and neurological examination. Age of onset; precipitating factors; details of the onset and evolution of the event by the patient and observer; history of tongue biting and urinary and fecal incontinence; history of any postevent motor, sensory, or other features; and timing and duration of the event are all important for the diagnosis of a seizure. In addition, birth and developmental history and history of any significant childhood illnesses, febrile seizures, head trauma, and drug and alcohol use are important. The clinical evaluation is followed by appropriate testing, which is directed toward diagnosis of seizures as well as checking into the possibility of other disorders that can mimic seizures.

### EEG/vEEG Monitoring

After a detailed history and examination, a routine EEG with hyperventilation and photic stimulation is one of the initial steps in diagnosing a seizure disorder. While an abnormal EEG showing epileptiform discharges is helpful, absence of epileptiform abnormalities does not rule out the possibility of a seizure disorder. A sleep-deprived EEG may be helpful if abnormalities are not seen in the awake tracing. If the patient is having frequent episodes, vEEG monitoring is an excellent way to evaluate the nature of the episodes. In fact, this type of monitoring, especially in patients with frequent

events, is most helpful in the diagnosis of a seizure disorder and distinguishing it from other conditions noted earlier.

### Cardiac Tests

A routine ECG or a Holter monitor may help in the diagnoses of cardiac arrhythmias. Orthostatic blood pressure testing and tilt table testing may be helpful in diagnosing patients with syncope. Patients with a cardiac murmur may benefit from the performance of an echocardiogram that may reveal the evidence of aortic stenosis or cardiomyopathies.

### Polysomnography

An overnight polysomnography (PSG) is helpful in understanding the nature of nocturnal episodes such as night terrors, sleep walking, RBD, and other abnormal movements during the night. In addition, PSG and MSLT can help in the diagnosis of narcolepsy.

### Neuroimaging

MRI may show evidence of structural brain abnormalities such as mesial temporal sclerosis, gyral abnormalities, heterotopias, or other findings that may suggest the possible epileptogenic focus. As with EEG, MRI scans help to make the diagnosis of epilepsy rather than rule out the possibility of nonepileptic events. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) scans may show hypometabolism and hypoperfusion during interictal periods or ictal focal hyperperfusion in patients with seizure disorder.

### Prolactin Levels

Increased prolactin levels may occur after a seizure and have also been used as a differentiating test. However, there are limitations (31) as this elevation of prolactin levels does not occur with all seizures and tends to occur more often in patients with medial temporal-onset seizures. Therefore, this test cannot reliably differentiate seizures from psychogenic events.

### Psychological and Psychiatric Evaluation

Neuropsychological testing and psychiatric evaluation may be more helpful in diagnosing underlying psychological or psychiatric conditions contributing to PNES. Some patients may have typical findings on certain neuropsychological tests that can help confirm the diagnosis.

While the understanding of the presentation of seizures has improved remarkably with the emergence of vEEG monitoring, differentiating seizures from nonepileptic

events can nevertheless pose significant challenges. Based on the presentation, a wide range of medical, neurological, and psychiatric conditions need to be considered. A detailed history from the patient and the observer is critical. vEEG monitoring has helped tremendously with the identification of seizures and seizure-like nonepileptic events. Accurate identification of seizure mimickers is paramount to institute the right treatment and prevent undue interventions.

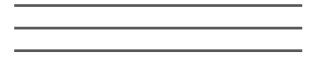
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P A R T



# Diagnostic Evaluation





# Clinical Evaluation

*Aatif M. Husain and Abeer J. Hani*

## 9

### C H A P T E R

The clinical evaluation of epilepsy patients, like any other patient, involves a careful review of the history, thorough examination, and directed laboratory and neuroimaging studies. However, there are certain unique characteristics of an epilepsy evaluation that set it apart from not only other medical conditions, but also other neurologic conditions. Whereas history from the patient is very important, arguably even more important is observer history from a family member or friend of the epilepsy patient. The observer can provide details of the seizures that the patient cannot provide. The examination provides further clues about whether a brain disorder or lesion is present. Neurologic examination is important, as well as general physical and skin examinations. EEG and neuroimaging evaluation are also very important, and depending on the clinical situation, magnetic resonance imaging (MRI) or computed tomography (CT) may be more appropriate. Laboratory testing helps exclude possible provoking factors for seizures, and occasionally, particularly in pediatrics, may lead to a neurologic or metabolic disorder causing seizures. The unique features of the clinical evaluation of an epilepsy patient will be discussed in further detail.

One of the main goals of the clinical evaluation is to classify the seizure type. Recently, the International League Against Epilepsy (ILAE) updated seizure classification (1). A summary of this classification is presented in Table 9.1. Once the seizure types are identified, the clinical evaluation can help determine the epilepsy syndrome. The classification of epilepsy syndromes is presented in Table 9.2. Details of these classifications are presented in Chapters 3 and 4.

In this chapter the patient's episodes are referred to as seizures. It is recognized that when initially evaluating a patient, it may not be clear if the episodes are indeed epileptic or nonepileptic seizures. Moreover, there is disagreement as to whether nonepileptic episodes should be called seizures, attacks, or spells (2). There are advantages and disadvantages for each of these terms, but in this chapter the term "seizure" will be used without implication of whether it is epileptic or not, unless otherwise specified.

### HISTORY

The history is the most important feature of the clinical evaluation of an epilepsy patient. Whereas the patient can describe many aspects of the history, she/he is necessarily a poor witness of the actual seizure. Since obtaining a description of the actual seizure is important, talking with a family member or friend who has seen the seizures is important. In addition to obtaining the basic demographic information, determining handedness is very important. This helps establish cerebral dominance, which, in turn, may help with localization of seizure onset.

### Description of Seizure(s)

The examiner must first determine how many different types of seizures the patient has experienced. The nature of each seizure type must be described. In addition, the age of onset, frequency, and evolution over time should be determined.

A detailed description of what happens to the patient during a seizure is very important to obtain. The various features of a seizure that should be noted are presented in Table 9.3. The presence of an aura should be determined. Mentation during an aura is not altered, and the patient is aware of their surroundings. An aura can be of various types, including various sensory hallucinations, light-headedness, déjà vu sensation, abnormal taste or sensation, or an indescribable sensation. The duration of the aura and the consistency with which the aura precedes the seizure should be noted. Most often the aura is followed quickly by the seizure, but sometimes auras occur in isolation and are only rarely followed by a seizure. By definition, an aura is a restricted, focal epileptic discharge. If the presence of an aura can be confirmed, it becomes very likely that the seizure is focal. The manifestation of the aura represents the site of onset of the ictal discharge.

An aura must be distinguished from a prodrome. The latter is a sense of being unwell or other vague sensation that can precede a seizure by minutes to days. The prodrome may be followed by an aura, which quickly leads to a seizure,

**TABLE 9.1 Classification of Seizures (Prior Classification Presented in Italics)**


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Focal seizures ( <i>partial seizures</i> )
Without impairment of consciousness or awareness ( <i>simple partial seizures</i> )
With observable motor or autonomic components
Involving subjective sensory or psychic phenomenon only ( <i>aura</i> )
With impairment of consciousness or awareness ( <i>dyscognitive</i> ) ( <i>complex partial seizures</i> )
Evolving to bilateral, convulsive seizure ( <i>secondarily generalized seizure</i> )
Generalized seizures
Tonic-clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Unknown
Epileptic spasms

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Source: Adapted from Ref. (1). Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 2010;51:676–685.

or the prodrome may eventually lead to a seizure directly. Whereas an aura is an epileptic phenomenon, a prodrome is not. A prodrome can occur with focal or generalized seizures, and does not help establish a site of onset of the ictal discharge.

The degree of mental status impairment during a seizure should be determined. When there is no impairment of consciousness or awareness, the presence of motor, sensory, or autonomic features is noted. These are the same as auras. In the previous ILAE classification, these were referred to as simple partial seizures (3). If the patient is unable to respond to surrounding, consciousness and awareness are altered, and the seizure is referred to as dyscognitive. Previously, these were called complex partial seizures. Various motor, autonomic, and other symptoms, such as tongue biting and incontinence, may also be present in seizures with altered consciousness, and their presence is noted. The motor activity may be in the form of automatisms of the hands or mouth, clonic activity, myoclonic jerks, falls, etc. These features help in localizing the site of onset of the seizure.

Various postictal phenomena are frequently noted, and their presence should be determined. These include fatigue, headaches, confusional state, and psychosis. The duration

**TABLE 9.2 Classification of Electroclinical Syndrome and Other Epilepsies Most Likely to be Seen in Veterans (Adult Patients)**


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Electroclinical syndrome arranged by age of onset
Adolescence – Adult
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with generalized tonic-clonic seizures alone
Progressive myoclonus epilepsies
Autosomal dominant epilepsy with auditory features
Other familial temporal lobe epilepsies
Less specific age relationship
Familial focal epilepsy with variable foci
Reflex epilepsies
Distinctive constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsions-hemiplegia-epilepsy
Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development
Neurocutaneous syndromes
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.

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Source: Adapted from Ref. (1). Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 2010;51:676–685.

of the seizure and the postictal phase should be determined, keeping in mind that seizures are terrifying events for family, friends, and onlookers, and that the duration of the event is frequently overestimated. Most seizures, whether focal or generalized, usually do not last longer than 60 to 90 seconds.

In children, the interviewer often has to rely on parental report for a description of the events of concern and to obtain information about seizure types, auras, ictal and postictal phases. Some children may have insight into their seizures and it is often worthwhile to get their version of the events. Postictally, it is not uncommon to have postictal Todd's paralysis in children with focal seizures and that may be a helpful localizing sign of seizure onset. It is often helpful to utilize this opportunity to teach family members about different seizure manifestations that they may look for during a seizure and to urge them to try to videotape the events of concern whenever feasible.

**TABLE 9.3 Features of a Seizure History and Description**

Aura
Olfactory hallucinations
Visual hallucinations
Auditory hallucinations
Light-headedness
Déjà vu
Abnormal taste
Abdominal sensation
Indescribable sensation
Duration of Aura
<30 sec
31–59 sec
1–5 min
>5 min
Mental status
Loss of awareness
Loss of consciousness
Aphasia
Motor Activity
Automatism (facial or manual)
Focal motor activity
Generalized motor activity
Focal to generalized motor activity
Sensory Symptoms
Paresthesia
Dysesthesia
Numbness
Autonomic Symptoms
Other Symptoms
Tongue biting
Incontinence
Postictal phase
Fatigue
Headache
Confusional state
Psychosis
Duration of seizures
<30 sec
31–59 sec
1–5 min
>5 min
Duration of postictal state
No postictal period
<5 min
5–30 min
>30 min

### Description of First Seizure

Details of the first recognized seizure should be sought from the patient and family members. All features discussed earlier about individual seizure types should be asked in reference to the first seizure. How this seizure type has evolved and whether it is still occurring should be determined. The examiner should appreciate that the first recognized seizure may not have been the first ever seizure. The first ever seizure may have been subtle, such as a brief staring spell, and not recognized as a seizure. Some patients only recognize

that they have epilepsy after a tonic–clonic seizure. This is not uncommon in children with childhood absence seizures whose absence seizures may go unrecognized for several months and are often brought to attention following a generalized tonic–clonic seizure.

### General Issues Relevant to Seizures

There are several other details of the patient's overall seizure history that should be determined. A summary of these is presented in Table 9.4. Sometimes seizures have specific triggers and their identification may have a significant impact on seizure control. Seizures may also have circadian triggers, occurring during a particular phase of the sleep–wake cycle, such as only upon awakening from sleep or only in sleep. These features, if identified, help narrow the epilepsy syndromic diagnosis. Whether seizures result in injuries should be noted, as this will help determine the safety advice that should be given to patients. In addition, fitness for driving and operating other machinery may be influenced by prior injuries. Patients should be questioned about a prior history of status epilepticus (SE). This information may help in localization of seizure onset and may affect medical management of these patients.

In children, seizure precautions, including avoiding contact sports and supervision during swimming and performing social activities should be reviewed. While ensuring a safe supervised environment for children with epilepsy, it is important to make sure that they are socially empowered to participate in nonrisky social activities.

Many epilepsy patients have a variety of sleep complaints and disorders. Daytime sleepiness is a common complaint and may be due to medications, sleep deprivation,

**TABLE 9.4 Other Seizure Details**

Triggers
Stress
Sleep deprivation
Infection/illness
Fasting
Illicit drugs
Alcohol use
Menstrual cycle
Flashing lights
Seizure occurrence time
Diurnal
Nocturnal
Upon awakening
No pattern
Injuries with seizures
Bruise
Laceration
Burn
Fracture
History of status epilepticus

or primary sleep disorder such as sleep apnea. Presence of untreated sleep apnea may result in greater difficulty in controlling seizures. Thus, asking patients about sleep complaints, in particular, symptoms of sleep apnea, is very important and may help in better managing these patients.

Mental health problems are common in epilepsy patients. Depression and anxiety should be specifically sought. Antiepileptic drugs (AEDs) may make these worse (or better in some cases). Untreated, mental health disorders can hinder adequate management of epilepsy patients, both by affecting quality of life and by reducing compliance with AEDs. In addition, mental health disorders commonly coexist with psychogenic nonepileptic seizures (PNES) (4).

Similarly, children with epilepsy often have associated comorbidities, including intellectual disability, cerebral palsy, attention deficit hyperactivity disorder (ADHD), autism, learning difficulties, and depression. These conditions may be handicapping and proper identification and treatment is paramount to improve the quality of life of these children.

### Etiology/Risk Factors

When a patient is first diagnosed with epilepsy, one of the foremost questions she/he has is, “Why did I have a seizure?” Every patient must be questioned about risk factors for seizures that may suggest an etiology. The etiology will ultimately be found only in a minority of patients with seizures, but that does not preclude a thorough evaluation. Common historical elements that the patient should be questioned about are presented in Table 9.5.

In adult patients, questions about childhood are often skipped, but these are very important and should be asked. This is of utmost importance in children presenting for evaluation of seizures. Birth-related history is important to determine: Was the delivery premature? Were there any congenital malformations? Were there any maternal illnesses, and was the delivery cesarean, vaginal, or forceps/suction assisted? Did the patient require admission to the neonatal intensive care at birth and why? How was the neonatal and infantile period? Did the patient reach her/his

**TABLE 9.5 Risk Factors for Seizures**

Maternal illness during pregnancy
Prematurity
Birth-related injury
Congenital malformations
Febrile seizures
Stroke
Tumor
Dementia
Meningitis
Encephalitis
Family history of seizures
Trauma
Other

**TABLE 9.6 Etiology of Seizures**

Viral, bacterial, and parasitic infections
Traumatic brain injury
Stroke
Intraventricular hemorrhage
Hypoxic-ischemic encephalopathy
Other metabolic or toxic insults
Neurocutaneous syndromes; Inborn errors of metabolism
Genetic and chromosomal development encephalopathies
Developmental encephalopathy of unknown cause as evidenced by the presence of mental retardation, cerebral palsy, or autism with no evidence of a specific insult of disorder to which cause can be attributed preceding the onset of epilepsy
Malformations of cortical or other brain development with or without known genetic determinants
Neoplasia
Mesial temporal sclerosis
Dementia
Other degenerative neurologic diseases
Genetic or presumed genetic
Epilepsy of unknown cause, without relevant abnormalities on examination, cognition, history, or imaging;
Other

Source: Adapted from Ref. (15). NINDS. NINDS common data elements: epilepsy [online]. [http://www.commondataelements.ninds.nih.gov/epilepsy.aspx#tab=Data\\_Standards](http://www.commondataelements.ninds.nih.gov/epilepsy.aspx#tab=Data_Standards). Accessed April 1, 2013.

neurodevelopmental milestones (including walking and talking) on time? Did she/he require any special services, including speech therapy, physical therapy, or occupational therapy during childhood? Childhood problems such as febrile seizures and educational difficulties should also be determined. Some conditions that can cause seizures are seen more often in adults, and these include strokes, brain tumors, and dementias. Presence of these should be sought. Infections such as encephalitis and meningitis can occur at any age and may be the cause of seizures. Family history of seizures should also be noted to determine if there is any genetic predisposition to seizures. After assessing these risk factors and completing the clinical evaluation, an etiology may be determined. Possible etiologies for seizures are presented in Table 9.6.

Traumatic brain injury (TBI) is a common cause of seizure in younger patients, keeping in mind that epilepsy can develop years after the trauma (5). Trauma-related questions that the examiner should attempt to get answers to are presented in Table 9.7. Most important questions that the patient may be able to answer are the severity and type of trauma. Establishing the approximate time of trauma is important as well.

### Prior Treatment

Questioning the patient about prior treatments is important. Ideally, the drug, dose, plasma concentrations achieved, any side effects, and reasons for discontinuation should be determined for each drug the patient has used in the past.



**TABLE 9.7 Traumatic Brain Injury and Epilepsy**

Cause of traumatic brain injury
Road traffic incident
Incidental fall
Other nonintentional injury
Violence/assault
Act of mass violence
Suicide attempt
Other
Severity of trauma
Mild (LOC < 30 minutes)
Moderate (LOC 30 minutes to 24 hours)
Severe (LOC > 24 hours)
Type of traumatic brain injury
Closed
Penetrating
Blast
Crush
Unknown
Other
Traumatic brain injury imaging results
Skull fracture
Epidural hematoma
Extraaxial hematoma
Subdural hematoma
Subarachnoid hemorrhage
Vascular dissection
Traumatic aneurysm
Venous sinus injury
Midline shift
Cisternal compression
Fourth ventricle shift/effacement
Contusion
Intracerebral hemorrhage
Intraventricular hemorrhage
Diffuse axonal injury
Traumatic axonal injury
Penetrating injury
Cervicomedullary junction/brainstem injury
Edema
Brain swelling (ie, hyperemia)
Ischemia/infarction/hypoxic ischemic injury
Brain atrophy/encephalomalacia
Other

Surgery needed for TBI?

Source: Adapted from Ref. (16). NINDS. NINDS common data elements: traumatic brain injury [online]. [http://www.commondataelements.ninds.nih.gov/tbi.aspx#tab=Data\\_Standards](http://www.commondataelements.ninds.nih.gov/tbi.aspx#tab=Data_Standards). Accessed April 1, 2013.

In addition, combination therapies that have been attempted should also be noted. Of course, in many situations, patients will not remember all the details of the medications they have tried previously. At a minimum, the name of each AED and why it was discontinued should be determined. If a medication caused a serious allergic reaction, that should be noted.

Many AEDs are available in generic formulation. The interviewer should try to determine if the patient was taking brand name or generic AEDs, and if there were any problems converting from brand to generic formulation. Having pictures of medications is helpful, as patients may only know their pills by their shape and color and not name.

Patients who have had difficult to control seizures may have had other types of treatments as well. These include vagus nerve stimulator (VNS), dietary therapy (such as the modified Atkins or ketogenic diet), or surgical treatment. Details of these therapies should be obtained from the patient or chart. In particular, the VNS should be interrogated and its settings noted.

Many patients use herbal medications and nutritional supplements with the belief that they improve general health and lessen side effects of AEDs. There is a general belief that these drugs do not cause side effects. In fact, many may interfere with AEDs and some may be proconvulsants. The examiner should identify which herbal medications and nutritional supplements the patient is using and their interactions with AEDs.

Many women with epilepsy are advised to take folic acid when they are prescribed an AED. This serves to reduce the risk of fetal malformations should the patient become pregnant while on an AED. Calcium/vitamin D is also prescribed to epilepsy patients, especially those on hepatic enzyme inducing AED. Adequate doses of calcium/vitamin D can prevent bone loss and reduce the risk of pathological fractures. Patients should be questioned about whether they are taking folic acid and calcium/vitamin D and their compliance with these medications.

### Other Medications and Allergies

Medication other than AEDs that the patient is taking should be determined. This includes both prescription and nonprescription drugs. Many such medications can have important drug–drug interactions with AEDs. In addition, AEDs may affect these other medications. An important example is reduced efficacy of oral contraceptive pills (OCP) and warfarin with some AEDs like carbamazepine and phenytoin. In addition, as noted earlier, herbal medications, nutritional supplements, and homeopathic medications that a patient is using should be determined.

Determining allergies to medications is important. AED allergies should be specifically determined, and an attempt should be made to distinguish a true allergy versus an untoward side effect that the patient interpreted as an allergy. Other medicinal allergies should also be prominently noted in the patient's chart.

### Previous Diagnostic Workup

Investigations that epilepsy patients have often undergone include EEG and MRI. EEG can be of many types, including routine, sleep deprived, ambulatory for 24 to 96 hours, and video EEG (vEEG) monitoring. Results of these tests should be obtained, and ideally the tracing should also be obtained and reviewed by appropriately qualified individuals. "Over interpretation" of EEG, ie, calling benign variants or variations of normal EEG patterns epileptiform is common and often leads to prolonged, unnecessary treatment with AEDs (6). In many cases, an "abnormal" EEG turns out to

simply show a benign pattern that is not epileptiform. Similarly, MRI results should be obtained. It is now common for patients to present with their MRI scans on media that can be reviewed by the examining clinician. As with EEG, MRI should be reviewed and if there is any doubt about the finding, it should be reviewed with a qualified neuroradiologist.

Several other types of tests may also have been performed, and should be inquired about. These include positron emission tomography (PET), ictal and interictal single photon emission computed tomography (SPECT), neuropsychological testing, and magnetoencephalography (MEG). It is unlikely that the patient will be able to provide results of these tests, and these should be obtained from their source. These tests are performed usually when surgical treatment for epilepsy is being contemplated, and consequently, only a small percentage of epilepsy patients undergo these procedures. In children, in addition to the aforementioned investigations, it may be important to inquire about previous metabolic and genetic workup done to uncover the etiology of their epilepsy.

### Other History

As with any other patient, an epilepsy patient's past medical, social, and family history should be determined. In addition, a review of systems should be conducted to elicit other medical issues that did not become evident during history taking. Positive findings should be explored further as indicated, or the patient should be told to discuss them with her/his primary care provider.

Important features in the social history that should be inquired about include level of education, living arrangements and marital status, current employment, and driving. Knowing the patient's level of education can help the examiner estimate whether substantial cognitive impairment is present, either due to the epilepsy, mental health problems, or medications. Living arrangements and marital status will dictate the degree of services a patient might require. Employment (or student) status and driving will provide an insight into the degree of independence and social integration within the community. A patient in school will be able to avail support services (financial and social) through the community. Most U.S. counties and schools have Vocational Rehabilitation councilors that can assist students with obtaining financial support from the state to attend school. This may be in the form of assistance with tuition, books, and supplies and room and board. In addition, they can assist patients with finding employment after completion of school. The patient's nicotine, caffeine, alcohol, and recreational drug use history should be noted. Many of these, especially caffeine and alcohol, can affect seizure control when used in excess.

Family history about epilepsy should be determined. This may already have been asked earlier when discussing risk factors for seizures. It is not enough to know that there is a family history of seizures, but which relatives were/are affected and the type of seizures they have is important

to establish. Not all patients will be able to provide these details. Family history of other significant medical conditions should also be determined.

## EXAMINATION

In addition to a general physical examination, a detailed neurological examination must also be conducted. The physical examination should focus on determining presence and severity of concomitant medical problems. In addition, examination of the skin, nails, eyes, and other organ systems can provide clues to the underlying epilepsy etiology. Skin examination for hemangiomas, hypopigmented lesions (seen better with ultraviolet light), or other cutaneous findings may also suggest certain neurocutaneous syndromes. Dysmorphic facial and body features may also provide clues to the presence of brain malformations. Fundoscopic examination helps look for retinal abnormalities that may be seen in association with brain malformations or storage diseases. In children, it is important to assess the head circumference for micro- or macrocephaly.

The purpose of a detailed neurological examination is to determine if a focal brain lesion is present. Such a focal lesion could serve as the focus of epileptic discharges. Focal findings on examination should be followed by appropriate neuroimaging studies to confirm the presence and determine the cause of the lesion. Presence of focal findings on examination makes it more likely that AEDs will need to be used, as discussed further.

## EPILEPSY-RELATED HEALTH SCREENING

Screening for medical conditions commonly coexisting with epilepsy is useful. The examiner may be alerted to potential problems that she/he may not have suspected, and because of the screening may be able to implement therapies that reduce future morbidity. Common conditions that are typically screened for in patients with epilepsy include depression (and suicidal ideation), quality of life, and bone health. In addition, in children, it is important to screen for learning disabilities, major depression, anxiety, and ADHD.

### Depression and Suicidal Ideation

Screening for depression can be performed by asking relevant questions while taking the history. Various brief questionnaires are also available that can be used by the examiner or given to the patient to complete. The Beck Depression Inventory (BDI) is an easy-to-use screen that can be given to patients to complete. The BDI score can be tallied to determine the presence and severity of depression. Patients should also be specifically questioned about suicidal ideation. This is also addressed in the BDI, as a question specifically addresses this. Asking about and documenting suicidality is important as all AED have this listed as a potential complication. Of course, if suicidality is elicited, appropriate treatment and referrals should ensue.

### Quality of Life

The limitations imposed by epilepsy, in particular, restrictions surrounding driving and compromised independence, can adversely impact quality of life. This can have a wide-ranging impact, including on mood, medication compliance, and seizure control. The Quality of Life in Epilepsy (QOLIE) questionnaire was developed to assess this issue. The QOLIE-89, QOLIE-31, and QOLIE-10 are validated measures having 89, 31, and 10 questions, respectively (7). The latest version of the QOLIE-10 is called the QOLIE-10-P. Whichever inventory is chosen can be completed by the patient before her/his appointment. Higher QOLIE-10-P scores represent better functioning, and if these are completed at regular intervals, changes in quality of life can be longitudinally evaluated.

### Bone Health

Bone health is a major public health concern. Reduced bone density can occur due to life style, increasing age, hormonal changes, lack of exercise, medications, and many other reasons. This is common in older women, but epilepsy patients of all ages are particularly susceptible. Many AEDs, particularly enzyme-inducing AEDs, can increase bone loss, leading to osteopenia and in severe cases osteoporosis. Bone density is best evaluated by a dual energy x-ray absorptiometry (DEXA) scan. How frequently a DEXA scan should be performed in epilepsy patients varies depending on age and the AEDs, but generally it should be considered every 2 to 5 years. Measurement of serum vitamin D can be helpful when evaluating bone health. A low serum 25-hydroxy vitamin D level indicates a vitamin D deficiency. Supplementation should be recommended in these cases.

### Learning Disabilities

This is a common comorbidity seen in children with epilepsy. It is important to make sure that the patient's school is aware that the patient has epilepsy and that dedicated neuropsychological testing is performed. This would subsequently allow the parents and schoolteachers to negotiate an individualized educational plan tailored to the patient's need. The neuropsychological evaluation may need to be repeated over time as more learning difficulties are encountered. Career planning should also be based on the patient's capabilities and neuropsychological testing at times.

### Attention Deficit Hyperactivity Disorder

It is not uncommon for patients with epilepsy to have a prior diagnosis of ADHD or to develop ADHD symptoms following the onset of their seizures and with the use of various AEDs. The hyperactivity and concentration difficulties can be very disruptive and impact the patient's quality of life. In such cases, the use of stimulants is encouraged, especially in patients with controlled epilepsy. However, it

is important to inform the caregivers of the risk of exacerbating the child's seizures, given that stimulants are known to decrease seizure threshold. The decision to start AEDs in poorly controlled epilepsy should be determined by the expected risk-benefit ratio. In case seizures are worsened, another class of stimulants may be tried along with optimization of the AED regimen.

## INVESTIGATIONS

The most important investigations that are typically performed on patients with epilepsy are EEG and MRI. There are several types of EEG that can be done, and various neuroimaging tests other than MRI can also be performed to diagnose epilepsy and localize site of seizure onset. In addition, serological tests, in particular, AED serum concentration determinations, are important adjuncts to the clinical evaluation of epilepsy.

### EEG

An EEG is one of the most important tests that can be performed on a patient with epilepsy. Epileptiform activity can be detected on EEG, which greatly increases the likelihood that the patient has epileptic seizures. However, sometimes, several EEG need to be obtained before a convincing epileptiform activity is detected.

Many different types of EEG can be performed. A routine EEG is a 20- to 30-minute recording, while a sleep-deprived EEG is done after a full night or 24 hours of staying awake. This increases the probability of capturing epileptiform activity. Ambulatory EEG is a tracing in which electrodes are applied to the scalp in the EEG laboratory and then the patient is sent home. After 24 to 96 hours, the patient returns to the laboratory to bring back the machine and have their data downloaded. With ambulatory EEG, the odds of capturing epileptiform activity increases as the amount of data recorded is much greater than a routine EEG. vEEG monitoring encompasses admission to the hospital and recording video and EEG until the patient has a typical event. This latter type of testing can help characterize whether the event is an epileptic seizure and determine its site of origin. The value of EEG is discussed in Chapter 12.

### Neuroimaging

An imaging study of the brain is indicated in patients suspected of having seizures. MRI is the preferred technique for brain imaging, and several MRI protocols have been developed to evaluate specifically for seizures. These protocols include special cuts and sequences that better evaluate those parts of the brain that are most likely to be the sites of seizure onset, such as the temporal lobes. A CT scan may be used to evaluate the brain when there is a contraindication to performing an MRI. When a patient presents emergently, a CT scan may be appropriate if there is an abnormal

neurological examination, history of head injury, or a focal seizure onset (8). Other types of neuroimaging studies, such as PET, SPECT, MEG, and functional MRI (fMRI) can also be used when evaluating a patient for epilepsy surgery. Details about MRI and other neuroimaging studies are discussed in Chapters 20 and 21. In children, magnetic resonance spectroscopy may be used in selected cases to evaluate for certain etiologies, like elevated lactate (seen in mitochondrial disease) or decreased creatine (seen in creatine synthesis/transport disorders).

### Other Laboratory Tests

Other types of laboratory tests, such as serological, urine, or cerebrospinal fluid (CSF), should be performed as dictated by the history. Abnormalities in serum chemistries, particularly sodium and glucose, may cause seizures. Cell counts may suggest an infection. Urine and serum toxicology screen should be considered if there is a suggestion that recreational drugs could have caused the seizure. A CSF evaluation will not be needed in many patients, and clinical circumstances, such as an unexplained infection, will dictate if this is obtained (9). A serum prolactin level can help distinguish an epileptic from a nonepileptic seizure. An elevated serum prolactin level obtained within 20 minutes of a generalized tonic-clonic seizure has a high sensitivity for the episode being epileptic (10). A 25-hydroxy vitamin D level should be considered if bone health issues are present, as discussed earlier.

Serological tests are also used to monitor AED use. Serum concentrations for many AEDs can be measured. Care must be exercised to not try to dose AED so that plasma concentrations are within the “normal range.” AED dose should be adjusted to seizure control without side effects, whatever the plasma concentration may be. Checking plasma concentrations also aids in determining compliance of a patient with a prescribed AED therapy. Liver function tests, serum chemistries, and cell counts are also obtained to monitor potential adverse consequences of AED.

Based on the age of onset, seizure semiology, EEG, and other associated clinical features, it may be important to extend the workup to include evaluation for an underlying metabolic, genetic, and/or neurodegenerative condition. While each workup needs to be tailored to the specific clinical presentation, Table 9.8 highlights some of the investigations that may be considered (11). In addition, with the exponential advance in the genetic testing, many isolated gene analysis panels, epilepsy gene panels, and whole exome sequencing are now available for the workup of a suspected genetic epilepsy. It is recommended that genetic/metabolic testing be performed in coordination with metabolic/genetics specialists.

Specialized tests such as neuropsychological testing and sodium amytal (Wada) test are typically performed when surgical treatment is being considered. Neuropsychological testing may sometimes also be obtained to evaluate memory or mood-related issues in epilepsy patients.

## DIAGNOSIS

After a complete evaluation, a diagnosis must be determined. If possible, seizures should be classified according to the most recent ILAE classification. In addition, the epilepsy syndrome should be determined. If the spells are nonepileptic, they should be noted as such. Also, whether the spell is psychogenic, nonepileptic, or some other type of nonepileptic spell (such as a sleep disorder or a syncopal event) should be specified.

### EVALUATION OF FIRST SEIZURE

Many patients are brought to the emergency department after their first seizure. Others are seen by their primary care provider. A thorough evaluation is needed regardless of the setting in which the patient is seen. A thorough history must be obtained and examination conducted. Many of the history and examination items discussed earlier should be obtained, and ideally an observer should be questioned about what happened during the spell. Any provoking factors, such as sleep deprivation, trauma, infections, alcohol, and recreational drugs, should be sought. If no provoking factors are identified, the seizure is considered the “first unprovoked seizure.” Serological tests, including cell counts, serum chemistries, and toxicology screens, should be considered. Neuroimaging should be obtained. In urgent settings, often only a CT scan of the brain is available. Acute neurological events, such as hemorrhage and trauma, can be evaluated well with a CT scan. The patient should be referred for an MRI scan as soon as possible, however. A routine EEG should also be obtained as soon as possible. Many patients will benefit from neurological consultation. Guidelines for evaluation of first unprovoked seizures have been published (9,12).

Whether AEDs are started after the first unprovoked seizure depends on the clinical circumstances. In most instances, treatment is withheld unless the neurological examination is abnormal, there is a history of chronic static encephalopathy, the EEG shows clear epileptiform abnormalities, or the MRI demonstrates a lesion that could generate seizures. If the decision is made to start an AED, the clinician has many choices, and the drug is picked based on the patient’s symptoms and diagnosis. Guidelines for treatment of first unprovoked seizure in children have been published (9,13).

Regardless of whether an AED is started after the first unprovoked seizure or not, the patient will require counseling about safety issues and driving. Driving restrictions and whether patients need to be reported to the driving authorities depends on the state.

### FOLLOW-UP EVALUATIONS

When an epilepsy patient returns for follow-up, certain features of the history are important to obtain. It is important to know how many seizures have occurred since the last visit. If



**TABLE 9.8 Selected Tests for the Workup of Metabolic Epilepsies**

TEST	ASSOCIATED DISEASE*
Blood tests	
Acylcarnitine profile	Fatty acid oxidation (FAO) disorders, organic acidemias
Amino acids	Amino acidopathies
Ammonia	Urea cycle defects
Total and free L-carnitine	Primary and secondary carnitine deficiencies
Biotinidase level	Biotinidase deficiency
Homocysteine	Homocysteinemia
Lactate	Mitochondrial disease
Lysosomal enzymes	Lysosomal storage diseases
Neuronal ceroid lipofuscinosis (NCL) enzymes	Neuronal ceroid lipofuscinosis
Pipecolic acid and alpha-aminoadipic semialdehyde (AASA)	Pyridoxine dependent epilepsy
Transferrin isoelectric focusing	Congenital disorders of glycosylation
Uric acid	Lesch-Nyhan disease
Very long chain fatty acids	Peroxisomal disorders
Urine tests	
Organic acids	Organic acidemias
Creatine/GAA	Creatine deficiency syndromes
Sulfocysteine	Sulfite oxidase Deficiency
Pipecolic acid and alpha-aminoadipic semialdehyde (AASA)	Pyridoxine-dependent epilepsy
Pterins	Tetrahydrobiopterin deficiency
Purine and pyrimidine panels	Inborn errors of purine and pyrimidine synthesis
CSF tests	
Amino acids	Glycine encephalopathy and serine synthesis defect
Glucose	Glucose-1-transporter deficiency
Lactate	Mitochondrial disease, FAO disorders
5-Methyltetrahydrofolate	Cerebral folate deficiency
Neopterin/Tetrahydrobiopterin	Tetrahydrobiopterin deficiencies
Neurotransmitter metabolites (HVA, 5-HIAA,3-OMD)	Neurotransmitter diseases
Organic acids (glycolate)	Glutaryl-CoA dehydrogenase deficiency
Pyridoxal-5-phosphate	Pyridoxal-5-phosphate dependent epilepsy
Succinyladenosine	Adenylosuccinate lyase deficiency
Biopsies	
Skin biopsy	NCL, Lafora disease
Muscle biopsy	Mitochondrial diseases

\*Most of the diseases listed are diagnosed using a multitude of these tests, however the most diagnostic test is listed in association with each disease.

Abbreviations: 3-OMD, 3-O-methyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanilic acid

Source: Adapted from Ref. (11). Pearl P. *Inherited metabolic epilepsies*. New York, NY: Demos Medical; 2012.

seizures have occurred, information on the circumstances in which they happen should be elicited. Particularly important to know is whether AED noncompliance, fevers, and infections or illicit drug use contributed to the seizures. If several seizures have occurred, the seizure frequency and duration

of each seizure should be noted. The type of seizures should be carefully documented and compared to previous seizure events to determine if new types of seizures have occurred.

It is best to encourage patients and family members to keep a diary to note their seizure. These diaries can be



simple sheets of paper- or electronic, cloud-based versions. Various electronic diaries are available for patients to log on to and note their seizures. One such electronic resource is [www.epilepsy.com](http://www.epilepsy.com).

The AED the patient is taking should be reconciled with what she/he been prescribed. Any changes to preparation (brand vs. generic) should be determined. Other medications should also be reviewed and any changes noted. The use of over-the-counter drugs, nutritional supplements, and herbal medications should be reviewed. In particular, use of calcium/vitamin D and folic acid should be noted and encouraged. Every patient should be asked about the side effects of any AED currently being taken.

The follow-up examination of an epilepsy patient is usually focused on eliciting signs of medication toxicity. These will typically include mood disturbances, rash, nystagmus, ataxia, and gait disturbance. Some medication may have idiosyncratic side effects that must be evaluated, such as visual fields for patients taking vigabatrin. Other aspects of the neurological examination should be conducted as dictated by the clinical circumstances.

Epilepsy-related health screening is important to consider at each visit. An assessment of the patient's mood is important, and the presence of depression should be evaluated. This can be a result of AEDs, epilepsy itself, or an unrelated comorbid condition. Depression-screening questionnaires, such as those discussed earlier, should be considered. Of course, if significant depression is identified, its relationship to AED should be determined. Referral to a mental health provider should also be considered. Quality-of-life questionnaires should also be administered if possible. The QOLIE-10-P discussed earlier provides a reasonable assessment of how the patient's quality of life is changing with their disease and treatment. The need for a DEXA scan to evaluate bone health should be evaluated. The frequency with which a DEXA scan is performed varies with the clinical situation, but it should be considered every 2 to 5 years. Along with a DEXA scan, a 25-hydroxy vitamin D level may be obtained.

Appropriate laboratory tests should be ordered. These may include serum AED concentrations or cell counts and chemistries to evaluate for medication toxicity. There are many other specialized tests that may be needed depending on the clinical scenario. Similarly, EEG and neuroimaging tests should be ordered as indicated. It is important to watch for evolution of the seizure types and development of comorbidities or new deficits that would require further evaluation to refine the diagnosis and guide treatment.

The most appropriate diagnosis should be listed. If this is different from the diagnosis in previous visits, that should be noted and discussed. Appropriate referrals should be made.

### PATIENT EDUCATION

Educating patients about their epilepsy and its consequences is one of the clinician's most important roles. Certainly, patients with new-onset seizures and also those with established

**TABLE 9.9 Epilepsy Patient Education**

Driving
Side effects of antiepileptic drug
Treatment compliance
Pregnancy
Contraception
Bone health
Safety issues
Mental health
Suicidal ideation
Sudden unexpected death in epilepsy (SUDEP)
Epilepsy education resources

epilepsy have many questions about why they have seizures, whether they lose "brain cells" with each seizures, psychosocial consequences, risk of passing on the epilepsy to their children, etc. In addition to answering these questions, the clinician should consider educating the patient on several other issues that are important to many patients with epilepsy. A list of these is presented in Table 9.9. All of these cannot be covered in a single visit, and follow-up visits should be used to continue to educate patients about their disorder.

### Driving

One of the most frequently asked questions is about driving. In general, patients whose seizures are not controlled are restricted from driving. However, in the United States, each state has different laws about how long a patient must be seizure free before they can resume/start driving. The practitioner should be aware what the regulations are in the state in which they practice. Several websites maintain up-to-date lists of these requirements sorted by state. One such example is the Epilepsy Foundation, whose website (<http://www.epilepsyfoundation.org/resources/drivingandtravel.cfm>) has this information. In addition to whether a patient should be driving, the clinician must be aware of the reporting rules of the state. Some states mandate that the treating clinician report any patient with seizures, whereas others allow reporting only if there is a significant public safety concern.

### Adverse Effects of Antiepileptic Drugs

Before any AED is prescribed, patients should be told of the typical side effects that they might experience. The frequency with which these side effects are seen should be mentioned as well. Some drugs have useful side effects, such as weight loss with topiramate, and these should be mentioned as well. In addition, any unusual and unusually severe side effects that could occur should be discussed with the patient. All AEDs have a warning about suicidality, and depression and

suicidality should be discussed with the patient. If anything can be done to mitigate the side effects of AEDs, that should be discussed as well. Potential interaction of AEDs with other medications the patient may be taking should be noted.

### **Treatment Compliance**

Treatment compliance should be stressed. The most common cause of breakthrough seizures is medication noncompliance. Patients should be encouraged to use items such as pill boxes to help them remember when to take their medications. In addition, services are available that will text patients when it is time to take their medication. In adolescents, treatment compliance can often be a serious problem. Adolescents with epilepsy should be carefully and nonjudgmentally counseled about their epilepsy and motivated to adhere to their medication regimen. At times, switching to a long-acting AED may be helpful in such cases.

### **Pregnancy and Contraception**

With women of childbearing potential, pregnancy and contraception issues must be discussed prior to initiating AED treatment. Some AEDs are more teratogenic than others, and the possible effect the selected AED can have on a fetus should be discussed with the patient. Why the particular drug was chosen should be shared with the patient as well. Folic acid use should be encouraged to minimize the risk of birth defects. Some AEDs interact with hormonal contraception and reduce their contraceptive efficacy. For women using hormonal contraception, whenever possible, AEDs that do not affect this should be used. If this is not possible, the patient should be clearly informed of the consequence and encouraged to seek alternate forms of contraception. Some AEDs, such as lamotrigine, do not reduce the efficacy of hormonal contraception; however, oral contraceptives increase the rate of its metabolism and result in lower plasma concentrations. In these cases, the lamotrigine dose may need to be increased.

### **Bone Health**

All patients should be counseled about bone health. Many factors can lead to reduced bone density, including epilepsy and AED use. The risk of developing osteopenia and osteoporosis depends on the AED, with enzyme-inducing AEDs, such as carbamazepine and phenytoin, carrying a higher risk. Ways to mitigate bone loss, such as with calcium/vitamin D supplementation, should be discussed and if indicated, starting the patient on such supplements. The need for a DEXA scan and 25-hydroxy vitamin D level should be discussed.

### **Safety Issues**

There are many safety issues that may need to be discussed with epilepsy patients. Which ones are discussed will depend on the patient's circumstances. Among the most important

safety concern is driving. Employment-related safety should also be reviewed. If the patient works in an environment in which she/he may be dangerous to one self or others should be discussed and addressed, and if necessary the patient should be removed from such a work environment. Some activities such as climbing on ladders and swimming unattended should not be allowed. Whereas safety issues are important to remind patients of, it should be recognized that safety concerns should not prevent epilepsy patients from leading full and productive lives.

### **Mental Health and Suicidal Ideation**

As noted previously, epilepsy and AEDs can adversely affect mental health, thus depression and anxiety disorder are common in epilepsy patients. Moreover, many psychiatric disorders such as PTSD may be linked to development of PNES. Treatment of the underlying disorder is imperative for recovery. Sometimes the severity of the mental health condition is such that the patient is suicidal. It should be recognized that all AEDs carry a heightened risk of suicidality and any AEDs that confer suicidal ideation should be immediately discontinued. It is not unusual for patients to require a referral to mental health experts for further evaluation and treatment.

### **Sudden Unexpected Death in Epilepsy**

The vast majority of epilepsy patients enjoy full and long lives. However, the risk of death is higher in epilepsy patients than in healthy peers. Death can occur due to an epilepsy-related accident, a severe medication-related adverse effect or due to the underlying condition. Sudden unexpected death in epilepsy (SUDEP) is one of the most common causes of premature death in epilepsy patients. It is more common in patients with generalized tonic-clonic seizures, refractory seizures, and in those with cognitive impairment. When SUDEP is discussed with patients and families depends on both the comfort of the practitioner in discussing this issue and the receptiveness of the patient in hearing about it. There is general agreement that it should be addressed at some point during treatment.

### **Epilepsy Education Resources**

There are many resources available for epilepsy patients. These include websites that provide education and other services (such as seizure calendars) and others that provide an avenue for advocacy and research. A brief list of such websites is presented in Table 9.10. Patients can be referred to these resources to learn about epilepsy, participate in advocacy, contribute to, or participate in research and connect with other patients with epilepsy. Governmental resources may be available for epilepsy patients as well. Vocational Rehabilitation services are available at many universities in many states and provide educational and vocational assistance.

**TABLE 9.10 Websites With Epilepsy Resources\***

RESOURCE	WEB ADDRESS	SERVICE PROVIDED
Epilepsy Foundation**	www.epilepsyfoundation.org	Education, information, research, advocacy, support
Epilepsy.com**	www.epilepsy.com	Education, information, research, advocacy, support
American Epilepsy Society	www.aesnet.org/patients	Information
Centers for Disease Control (CDC)	www.cdc.gov/epilepsy	Education, information
Citizens United for Research in Epilepsy (CURE)	www.cureepilepsy.org	Research, awareness, advocacy
Epilepsy Advocate	www.epilepsyadvocate.com	Education, information, scholarships
International League Against Epilepsy (ILAE)	www.ilae.org/Visitors/Centre/Index.cfm	Information
Patients Like Me	www.patientslikeme.com/conditions/3-epilepsy	Social media, education, information
National Institute of Neurological Disorders and Stroke (NINDS)	www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm	Education, information, research
Veterans Affairs Epilepsy Centers of Excellence	www.epilepsy.va.gov	Education, information

\*This is an incomplete list. There are many more organizations and websites that provide education, information, and other services to patients with epilepsy.

\*\*Most useful websites for patients with epilepsy.

## EPILEPSY QUALITY MEASURES

The American Academy of Neurology (AAN) has developed quality measures for epilepsy (14). These measures were derived by reviewing literature for guidelines, recommendations, and expert statements on what constitutes high-quality care for epilepsy patients. Eight quality measures have been identified, and their implementation will likely improve the quality of care delivered to patients with epilepsy. These measures are presented in Table 9.11.

These quality measures summarize what is most important to assess in the clinical evaluation of patients with epilepsy. Seizure type and frequency must be determined. An attempt must be made to determine the etiology of seizures and identify the epilepsy syndrome if possible. An EEG and MRI or other neuroimaging study should be obtained or reviewed if previously performed. Patients should be queried about AED side effects. In those patients whose seizures are not controlled with medications, surgical therapy should be considered. Confirmatory vEEG monitoring to differentiate between epileptic and nonepileptic seizures should also be considered. Counseling patients about safety, in particular driving, is very important. In addition, appropriate counseling for women of childbearing potential is essential.

An orderly approach to the clinical evaluation of a patient with seizures is necessary to arrive at the correct diagnosis. A complete and thorough history and examination complemented by EEG and neuroimaging are most

**TABLE 9.11 AAN Epilepsy Quality Measures**

1. Seizure type and current seizure frequency
2. Documentation of etiology of epilepsy and epilepsy syndrome
3. EEG results reviewed, requested or test ordered
4. MRI/CT scan reviewed, requested or scan ordered
5. Querying and counseling about antiepileptic drug side effects
6. Surgical therapy referral consideration for intractable epilepsy
7. Counseling about epilepsy-specific safety issues
8. Counseling for women of childbearing potential with epilepsy

Source: Adapted from Ref. (14). Fountain NB, Van Ness PC, Swain-Eng R, et al. Quality improvement in neurology: AAN epilepsy quality measures: Report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. *Neurology*. 2011;76:94–99.

likely to provide the correct diagnosis. At times, a more extended workup to evaluate for metabolic and genetic epilepsies may be needed. At every visit the patient provides additional information that supplements their history and may further refine the assessment. Educating the patient about epilepsy, its consequences, and AED is an essential part of every clinical evaluation. The availability of quality measures provides a guide for practitioners regarding what is most important to assess in the clinical evaluation of epilepsy patients.

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# EEG Instrumentation

*Saurabh R. Sinha*

EEG involves the measurement of electrical fields generated by the activity of neurons and, possibly, glial cells in the brain. Electrodes are placed on the scalp and the EEG equipment is used to filter, amplify, store, and display the electrical potentials. The proper interpretation of EEG results requires an understanding of the generators of the electrical fields as well as the properties and limitations of the measurement equipment and procedures. In this chapter, basic information about the generators of cerebral potentials, basics of EEG instrumentation, and recording procedures will be reviewed.

## CEREBRAL GENERATORS OF EEG POTENTIALS

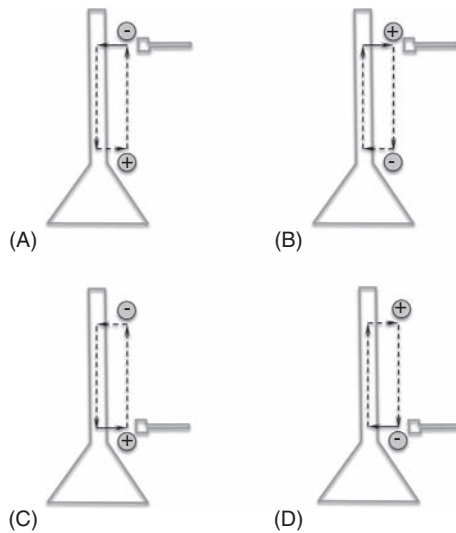
EEG measures neuronal activity at a relatively large scale. It represents the summated activity generated by large groups of neurons ( $10^5$  or more). Due to the need for summation of activity over a large population, the main source of EEG potentials are cortical neurons – their arrangement in layers with similar orientations (aligned with their long axis perpendicular to the cortical surface) allows for better summation of activity compared to other types of neurons with a more random orientation. For neurons with a more random orientation, even if their activity is synchronized, the activity may actually partially cancel each other out. In addition to spatial orientation of the neurons involved, the temporal scale of the activity is also important. For example, the duration of a neuronal action potential is approximately 1 msec. For summation to occur across a group of neurons, their firing would have to be very precisely synchronized (at the sub-millisecond level). This cannot occur over a large population of neurons. Thus, even though action potentials are of relatively high amplitude ( $\sim 100$  mV), they make very little contribution to the EEG signal. Instead, activities of longer durations are the main contributors to the EEG signal. These include both excitatory postsynaptic potentials (EPSPs), mainly mediated by the neurotransmitter glutamate, and inhibitory postsynaptic potentials (IPSPs), mainly mediated by the neurotransmitter gamma-aminobutyric acid (GABA). Although postsynaptic potentials have much

smaller amplitudes than action potentials (on the order of millivolts to tens of millivolts), their longer durations (tens of milliseconds and longer) lead to better summation. Some other activities that may contribute to the EEG signal include the slow afterhyperpolarization seen in neurons after a burst of action potentials, and even slower changes in glial membrane potentials that occur in response to changes in extracellular ionic concentrations, especially potassium ( $K^+$ ) ions.

The summation of activity is further complicated by the fact that it reflects the flow of current in the extracellular space. Neuronal activity results in the creation of current sources and current sinks, loops of current, and dipoles of electrical potential (a source of electric fields, idealized as a rod connecting a positive and a negative charge) (Figure 10.1). For example, an EPSP occurring in the dendrites of a pyramidal cell results from the influx of cations into the dendrites from the extracellular space, resulting in a current sink. To compensate, current leaves the neurons at other sites, for example, the soma, creating a current source. The circuit is completed by the flow of current in the extracellular space from the current source (soma) to the current sink (dendrites). Thus, an EPSP in the dendrites of a pyramidal cell creates a dipole that is positive at the soma and negative at the dendrites. On the other hand, an IPSP near the soma of a pyramidal cell results from the inflow of anions at the soma, creating a current source (inflow of anions is electrically the same as outflow of cations). Thus, it can be seen that an IPSP at the soma also results in a dipole that is positive at the soma and negative in the dendrites. Similarly, an EPSP near the soma or an IPSP near the dendrites will both result in a dipole that is negative at the soma and positive in the dendrites.

Another determinant of how cerebral activity will be reflected in the EEG is the location and orientation of the activity with respect to the recording electrode. If the dipole representing the cerebral activity is placed inside a sphere (to represent the head), the voltage at each point on the surface of the sphere will be a function of the distance from that point to the positive charge and the negative charge: the charge that is closer will have the bigger effect. Thus,



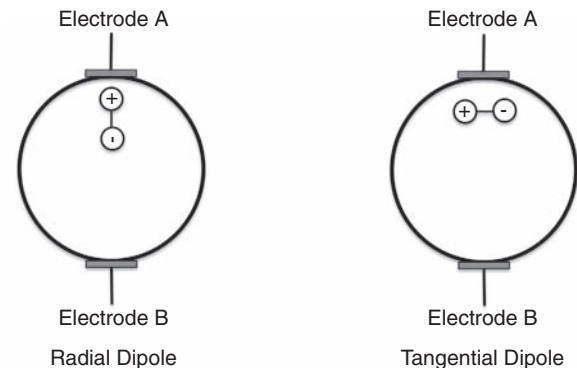


**FIGURE 10.1** Dipoles set up by excitatory and inhibitory inputs applied to different parts of a neuron. (A) Excitatory input in the dendrites sets up a dipole in the extracellular space that is positive at the soma and negative in the dendrites. (B) Inhibitory input in the dendrites sets up a dipole that is positive in the dendrites and negative at the soma. (C) Inhibitory input at the soma produces a dipole that is positive at the soma and negative in dendrite. (D) Excitatory input at the soma produces a dipole that is positive in the dendrites and negative at the soma.

points closer to the positive charge will have a relatively more positive voltage and points closer to the negative charge will have a relatively more negative voltage; points on the sphere that are equidistant from both charges will have zero voltage. Thus, for a radial dipole (one where the dipole is oriented radially out from the center of the sphere out), an electrode place directly above the dipole will have the maximum voltage that can be recorded (Figure 10.2). For a tangential dipole (one where the dipole is oriented parallel or tangential to the surface of the sphere), an electrode placed directly above the dipole will not record any voltage. These factors combined with the convoluted structure of the cerebral cortex, with its many sulci and gyri with different orientations, lead to a very complex relationship between cerebral activity and the recorded EEG signal. All of these issues make it very difficult to draw accurate conclusions about the nature of the underlying cerebral activity based on the EEG signal alone.

## EEG AMPLIFIERS

The voltages created by cerebral activity when measured with electrodes placed on the scalp are on the order of 10 to 100 mV. When measured directly at the cortical surface, these voltages are on the order of 10 mV. To accurately measure such small potentials, the EEG machine must have several components (Figure 10.3). These include electrodes placed

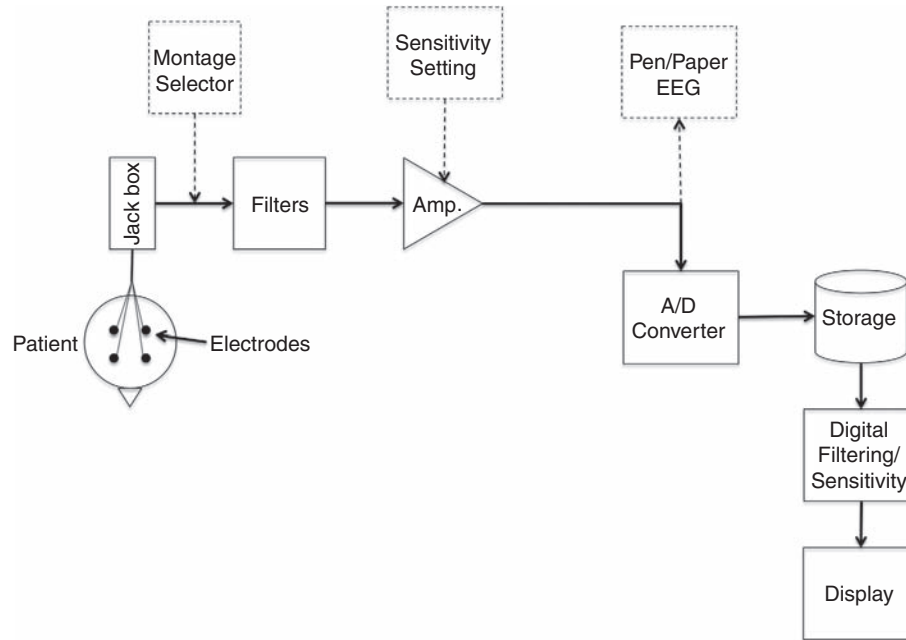


**FIGURE 10.2** For a radial dipole, as illustrated on the left, Electrode A will sense a relatively large positive potential, whereas Electrode B will sense a relatively small negative potential. This is due to its greater distance from the dipole. For a tangential dipole, as illustrated on the right, both electrodes will sense a neutral or zero voltage because both ends of the dipole are equidistant from the electrode.

on the scalp or cortex to sense the voltage and a jack box to connect wires from the electrodes to the EEG equipment. In older, analog EEG equipment, a montage selector is present to select which pair of electrodes is connected to a particular channel of the EEG amplifier. In digital EEG equipment, each electrode is recorded with respect to a common reference electrode; pairs of recorded channels are combined in the software to produce the desired montage. The activity from each electrode is then filtered (to remove unwanted activity and noise) and amplified (to increase the size of the activity). In analog machines, this signal is then translated into the deflection of a pen on a scrolling piece of paper. The paper speed determines how many seconds of EEG data will be plotted on each page – typical paper speeds are 30 mm/sec for EEG, although slower paper speeds like 10 mm/sec are used for neonatal recordings and for some longer studies. In digital machines, the activity is discretized (broken up into pieces) and digitized (converted to a numerical value) via an analog-to-digital (A/D) converter. The data are then stored on some form of permanent storage like a disk drive. The collected data can then be filtered and reformatted/combined in different ways and sent to a computer monitor for display.

## Electrodes

Various types of electrodes are used to record EEG signals. They are made of a conducting material, commonly metals with some underlying conductive paste or gel to improve contact with the skin. An ideal electrode should transduce the voltage underneath it without altering it in any way. However, real electrodes have limits on their performance, including the frequency range over which they are accurate and the buildup of charge on the electrode (polarization). Gold or gold-plated electrodes have commonly been used



**FIGURE 10.3** Schematic of EEG Amplifiers. Electrodes are placed on the patient's scalp and connected to a jack box. This is then connected to filters and amplifiers to condition and amplify the signal. The objects shown in dashed boxes are components of analog EEG equipment (montage selector, sensitivity settings and pen/paper EEG). Instead of pen/paper, for digital EEG equipment, the signal is digitized via an A/D converter, stored, and then reprocessed, if desired, prior to display on a monitor.

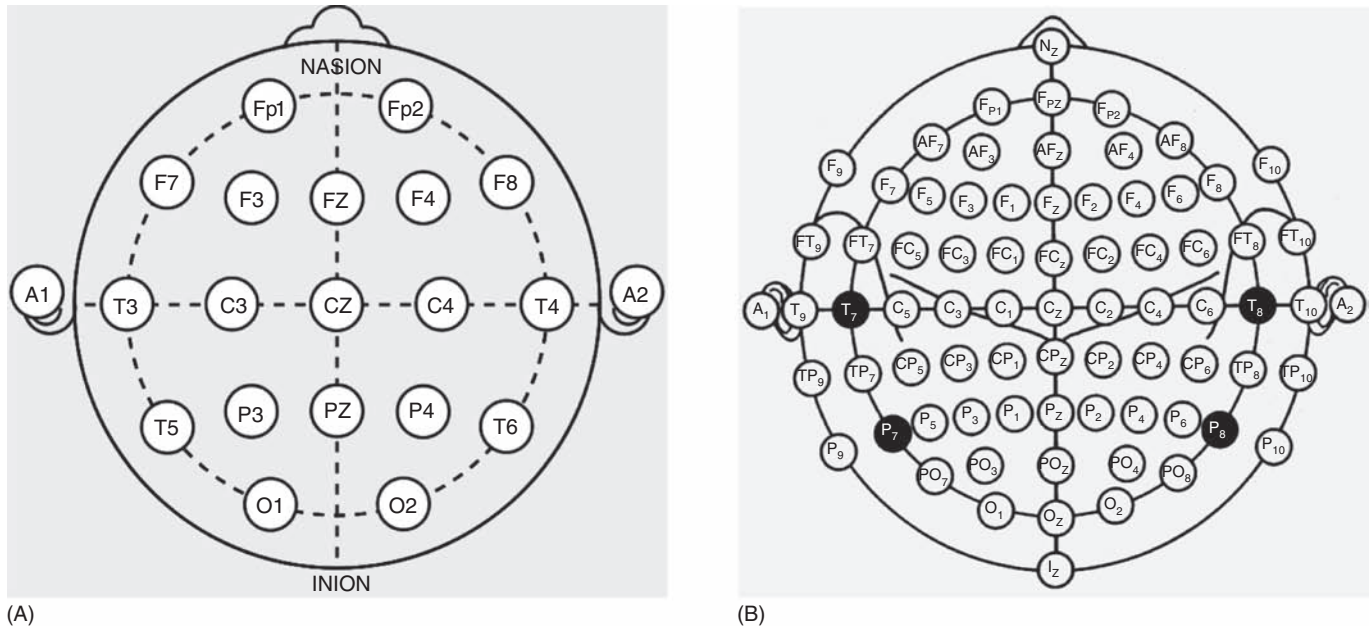
for scalp EEG recording, although electrodes made of conductive plastic or other disposable materials are gaining popularity due to concerns for infection and a desire for compatibility with imaging (CT and MRI). Subdermal needles and wires are also sometimes used for EEG recording. The earliest EEG electrodes were made from silver with a coating of AgCl, which offers a near-ideal combination of frequency response and lack of polarization; however, they are difficult to make and maintain and are no longer commonly used. For directly recording from the cortex, discs made out of metal are imbedded in plastic sheets with some of the metal exposed. For implanted electrodes, the discs are normally made from noble metals like platinum or platinum/iridium alloys; for acute use (ie, in the operating room only), stainless steel discs are sometimes used.

Electrode placement is important to understand. To capture the variation in cerebral activity in different parts of the brain, the EEG is recorded simultaneously from multiple locations on the head. Standardization of electrode locations is important for reproducibility of EEG signal across repeated studies on the same patient and across patients. The committee of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) recommends a specific system of electrode placement for use in all laboratories (Figure 10.4A) (1). This system is known as the International 10-20 system. Specific measurements are made based on bony landmarks (nasion,inion, and preauricular point) to determine the placement

of electrodes. From these landmarks, specific measurements are made and then 10% and 20% of a specified distance is used as the interelectrode interval. Uniform interelectrode distances and symmetric placement of electrodes over the left and right hemispheres are important for EEG interpretation.

The American Clinical Neurophysiology Society (ACNS) has recommended using a minimum of 21 electrodes from the International 10-20 system. Each electrode is named by a letter/number combination. The letter designates the approximate anatomical location ("F" for frontal, "T" for temporal, "Fp" for frontopolar, "C" for central, "P" for parietal, and "O" for occipital). Odd-numbered electrodes are placed over the left side of the head and even-numbered electrodes are placed over the right. In general, smaller numbers are closer to the midline (with "z" indicating zero being in the midline) and larger numbers are more lateral.

In 1991, the American Electroencephalographic Society added nomenclature guidelines for 75 electrode positions along five anteroposterior planes, lateral to the midline chain of 11 specific sites (Figure 10.4B). In addition, there are eight coronal chains (four anterior and four posterior to the chain of 13 electrode sites between the earlobe electrodes along the midline through the Cz electrode). Several electrodes are named differently in the 10-20 system and the extended nomenclature (the 10% or 10-10 system). Electrodes T3 and T4 in the 10-20 system are referred to as T7 and T8 in the expanded system, and T5 and T6 are referred to as P7 and



**FIGURE 10.4** (A) International 10-20 system for electrode placement. (B) 10-10 or 10% system for electrode placement. Electrodes in black have different names from the corresponding electrodes of the International 10-20 system (T7 = T3; T8 = T4; P7 = T5; P8 = T6).

P8. For infants, fewer electrodes are used and the precise number is somewhat variable from laboratory to laboratory. The ACNS has suggested using at minimum Fp1, Fp2, C3, Cz, C4, T3, T4, O1, O2, A1, and A2 (4).

### Filters

The biological signal must be filtered to optimize recording quality. Filtering refers to selectively removing activity within a certain frequency range from the overall signal. The ultimate goal of filtering is to remove activity that is not of interest. For example, very slow drifts in voltage-related sweating or changes in temperature or very fast activity related to muscle twitches and electrical interference. A secondary objective is to remove activity that may compromise performance of the EEG equipment. For example, very slow signals are distorted by commonly used electrodes, leading to artifacts. Similarly, very fast signals may exceed the maximum speed of pen deflection for analog equipment or sampling/display for digital equipment (discussed further). Taking these factors into account, scalp EEG recordings have traditionally been restricted to the frequency range of 0.5 to 70 Hz; intracranial recordings usually extend up to 200 Hz or higher. There is growing interest in recording both scalp and intracranial EEG at much higher frequencies (approaching 1000 Hz).

Most EEG equipment manufacturers describe filters in terms of the cutoff frequency,  $f_c$ ; this is the frequency at which the filter attenuates the power applied to the input by 50%. In terms of voltage, this equates to a drop of 29.3% or -3 dB. Thus, for a low-pass or high-frequency filter, at  $f_c$  the

output voltage will be 70% of the input voltage with greater attenuation above that frequency and much less or no attenuation below that frequency. For high-pass or low-frequency filters, frequencies below  $f_c$  are attenuated by greater than 70% and frequencies above  $f_c$  are attenuated much less. Some manufacturers describe high-pass filters in terms of time constants ( $\tau$ ):

$$f_c = \frac{1}{2\pi\tau}.$$

Thus, a time constant of 0.16 sec is equivalent to an  $f_c$  of 1 Hz. Commonly used filter settings include low-frequency filters (high-pass filters) of 0.1 to 1 Hz and high-frequency filters (low-pass filters) of 50 to 100 Hz. Another commonly used filter is the notch filter, which selectively attenuates the signals at/around its characteristic frequency. This is used to selectively remove interference from electrical equipment connected to power lines (60 Hz in the United States and 50 Hz in most other countries).

Filters attenuate signals of a given frequency regardless of their source; thus, they can distort the activity of interest just as easily as filtering out noise. Beyond attenuating selected frequencies, filters also introduce subtle changes in the timing of the recorded signal. High-frequency filters will introduce a small time lag: the activity will appear to occur at a slightly later time than it actually did. Low-frequency filters will introduce a small time lead: the activity will appear to occur at a slightly earlier time than it actually did. Thus, filters have the potential to distort signals in unintended ways, including filtering out activity of interest and

distorting artifactual activity so that it appears to be real. If filtering is differentially applied to different channels of an EEG, it may even distort the temporal relationships in the activity recorded by different channels.

### Differential Amplifier

Due to the low amplitudes of the EEG signal, it is necessary to amplify the potential of interest while ideally rejecting or reducing voltages from other sources, such as nearby electrical equipment and other biological sources like the heart. All EEG amplifiers are differential amplifiers. A differential amplifier takes two input voltages and produces an output that is an amplified version of the difference between the two inputs (Figure 10.5). The amplification factor or gain ( $A$ ) of most EEG amplifiers is on the order of  $1 \times 10^5$  to  $1 \times 10^6$  (adjustable); thus, an activity of 1 mV will be amplified at the output to 100 mV to 1 V. An ideal differential amplifier produces an output of 0 V when the two inputs are equal; however, real-world amplifiers have a nonzero output even when the exact same voltage is applied to both inputs. Thus, in addition to its amplification factor ( $A$ ), a differential amplifier is characterized by its common-mode rejection ratio (CMRR):

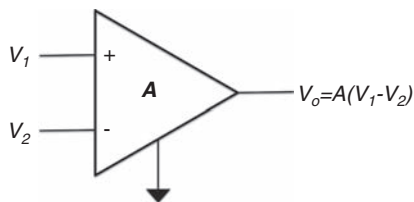
$$\text{CMRR} = \frac{V_{\text{out}} | (V_1 = 1, V_2 = 0)}{V_{\text{out}} | (V_1 = V_2 = 1)}.$$

Both amplification and CMRRs are usually expressed in decibels (dB):

$$A(\text{dB}) = 20 \log_{10} (A).$$

Thus, an amplifier with a gain of 100,000 has an amplification of 100 dB. Modern EEG amplifiers have CMRRs of greater than 80 dB, typically greater than 100 dB.

Although gain or amplification factor describes the actual amplification of the biological signal by the EEG amplifier, sensitivity is usually a more meaningful measure of signal amplification. The sensitivity is expressed in mV/mm (less commonly, mV/cm): it describes the amplitude in microvolts that would have to be applied to the inputs of the amplifier to result in a deflection of 1 mm on the output device. For analog EEG amplifiers, the output was deflection of an ink pen on paper.



**FIGURE 10.5** Schematic of a differential amplifier. The output ( $V_o$ ) is equal to the gain ( $A$ ) times the difference in the voltages at the two inputs ( $V_1 - V_2$ ).

$$\text{Deflection (mm)} = \frac{\text{Input } (\mu\text{V})}{\text{Sensitivity } (\mu\text{V/mm})}.$$

Thus, for a typical sensitivity of 7 mV/mm, 50 mV applied at the input would result in a pen deflection of 7.1 mm. For an analog amplifier, sensitivity can only be changed during the actual data collection by directly changing the gain of the amplifier. For a digital EEG amplifier/equipment, the sensitivity can also be changed mathematically after data collection is completed. The output for digital amplifiers is typically a deflection on a monitor; if the equipment is not calibrated for the specific monitor, the exact number of millimeters may not be accurate.

The polarity convention of the amplifier is important to understand. The two inputs to an amplifier are designated input terminal 1 and input terminal 2, and have historically been referred to as “G1” and “G2.” By convention, an upward deflection occurs when input 1 is more negative than input 2 or when input 2 is more positive than input 1. The polarity convention also specifies that the 10-20 electrode names, separated by a dash, designate electrodes connected to the two inputs of a differential amplifier (“electrode 1”—“electrode 2”), with “electrode 1” connected to input 1 and “electrode 2” connected to input 2.

### DIGITAL EQUIPMENT

A major advance over the past 25 years has been a change from analog to digital EEG equipment. Digital EEG equipment offers many advantages over analog equipment, the chief of which is the ability to reprocess the data after it has been collected. For analog EEG, decisions about electrodes, montages, filter settings, sensitivity settings, and paper speed settings have to be made during data collection; once the collected data is recorded on paper, it cannot be changed. By comparison, in digital EEG, extensive postcollection processing is possible, including combining the electrodes in different combinations to view the data in a different montage, filtering, change in sensitivity, and time scale. While this has reduced the importance of optimal selection of montages and filter/sensitivity settings during the data collection, it is still essential to have trained EEG technologists performing and attending to the data as it is collected. Even extensive postprocessing cannot compensate for misplaced or noisy electrodes, clinical observations, or the failure to use additional electrodes that may clarify a particular EEG finding. Another advantage of digital EEG is the ability to record data at significantly higher temporal resolution than is possible with analog systems. The pen and paper output is inherently limited with respect to frequency: the pen can move only at some maximal rate, limiting the maximum frequency of activity that can be displayed.

The main potential disadvantage to digital EEG is that it requires the conversion of the EEG to a digital signal. The analog EEG signal is continuous in terms of amplitude and time. Digitization requires this signal to be discretized in



amplitude and time. In terms of amplitude, the voltage range must be divided into discrete steps. The size of the steps depends on the input voltage range and the number of bits used to represent the data. For example, if the input voltage range of an A/D converter is -5 V to +5 V (for a total range of 10 V) and the resolution of the A/D converter is 16 bits (ie, 16 bits of data are used to represent a number), then the 10 V is divided over 65,536 steps ( $2^{16}$ ). The voltage resolution then becomes  $\sim 152$  mV ( $10/2^{16}$ ). Modern EEG machines typically have 16 bit or even higher resolution, which is more than adequate for most applications; however, older equipment was often limited to 8 or 12 bits and voltage resolution was a limiting factor in some cases.

Just as the bit resolution of the A/D converter determines the smallest amplitude difference that the equipment can resolve, the digitization rate of the A/D converter determines the fastest changing signal that can be resolved. The Nyquist theorem states that a signal must be sampled at a rate that is at least twice the fastest frequency that is present in the signal. If this is not done, a phenomenon called aliasing occurs and the apparent frequency of the recorded signal will be different from that of the actual signal. So, a sampling rate that is twice the fastest frequency present is the minimum required temporal resolution to avoid aliasing. For this reason, the EEG activity must be filtered to remove very high frequencies prior to A/D conversion. To represent the signal well, sampling rates of 2 to 3 times the highest frequency are usually needed. In modern EEG equipment, sampling rates usually exceed 400 Hz/channel, allowing for the recording of signals up to 200 Hz without aliasing and up to 100 Hz with good representation. Higher sampling rates are usually desirable for intracranial recording, especially if one is interested in recording high-frequency activity like fast ripples.

Another potential resolution issue is that of the monitor used to display the EEG data. The number of pixels displayed per inch should be adequate to display all the data points collected. For example, if the EEG is being displayed at a speed of 30 mm/sec and the EEG was sampled at a rate of 400 Hz, the horizontal resolution of the monitor should be enough to allow display of 400 points in 30 mm: 338 pixels or dots/inch. Modern monitors have resolutions that far exceed this requirement; but even their capabilities may be exceeded by signals sampled at very high rates, such as sometimes used for intracranial recordings, or if signals are displayed at very slow paper speeds. In this case, the software may only plot selected data points or may smooth the signal (average together adjacent points) for display. Thus, it is important to keep in mind that the displayed signal may not always truly represent the recorded signal.

### ELECTRICAL SAFETY

The risk of injury from EEG recording is very low, but proper safety procedures are still essential. The best predictor of injury is the amount of current or charge delivered to tissue. Current can cause pain and burns when delivered to the skin. If delivered to the heart, it can even produce

fatal arrhythmias. Currents as small as 0.1 mA (milliamp) can cause ventricular fibrillation if delivered directly to the heart. Applied through the skin, the pain threshold is typically about 1 mA and currents on the order of greater than 10 mA are required to cause injury (although factors like duration of current and area over which it is delivered are important).

There are several sources of potential unintentional delivery of current to a person from an electronic/electrical device. Any current will flow through the path of least resistance to the ground. Proper equipment and technique will avoid the situation where the path of least resistance goes through the patient or other people. Proper grounding of all medical equipment is essential. All medical equipment should be connected to a ground (the third prong of a three-prong plug is actually physically connected to the ground somewhere in the building). This allows any stray currents generated in the equipment to flow directly through to the ground and not through the patient or other people near the equipment. If multiple pieces of equipment are connected to a single patient, it is important that all equipment is connected to a common ground. If the ground points are different, then the path of least resistance may be through the patient to the ground of another piece of equipment. By ensuring that all equipment shares the same ground, stray current should flow directly to the ground from each piece of equipment.

Another source of potentially injurious currents is so-called leakage currents, which are due to stray capacitance or inductances that lead to a buildup of charge on equipment. Proper insulation of wires and grounding of equipment will minimize leakage currents. The level of contact a person has with equipment determines the maximum allowable leakage current (2). The highest risk group is neonates and patients with indwelling catheters or other medical devices: maximum allowable leakage current is 10  $\mu$ A. The intermediate risk group is patients with electrodes attached to the skin but no indwelling devices: maximum allowable leakage current is 100  $\mu$ A. The lowest risk group is those with only intermittent or casual contact with the equipment: maximum allowable leakage current is 500  $\mu$ A.

### RECORDING PROCEDURES

The suggested procedure for actually recording the EEG has been laid out in guidelines (3). The technologist first measures the head to find the appropriate location for the electrodes. For most scalp EEG recording, a minimum of 16 and usually 21 electrodes are used (including A1, A2, Fz, Cz, and Pz). The skin must be prepped using cleaning solution and a mild abrasive. This insures good contact with the electrode. The electrodes are then applied using a conductive paste or gel and plugged into the jack box. Appropriate filter settings (usually 0.5 Hz low-frequency filter, 70 Hz high-frequency filter, and no notch filter), sensitivity settings (typically 5–15 mV/mm), and paper speed (30 mm/sec) are set. An impedance check and square wave



calibration are performed. The impedance check tests the resistance between each electrode and a reference electrode. The impedance should be below 5 k $\Omega$  for all electrodes: higher impedances suggest poor contact and produce noisier signals. Impedances below 100  $\Omega$  suggest a short circuit. In addition to avoiding impedances that are too high or too low, it is ideal to have impedances that are well matched, that is, similar across all electrodes. Mismatched impedances lead to mismatch in the input to the differential amplifiers and compromise the cancellation of signals that are common to the two inputs. Square wave calibration consists of applying a series of square waves of a known voltage to each amplifier. If the filters and sensitivities of the amplifiers are correct, the output should be the same for all channels. In analog EEG machines, it was also important to perform a biological calibration (biocal), which consisted of applying the same pair of electrodes (often Fp1—O2) as inputs to all the amplifiers; again, the outputs should be the same, testing the response of the amplifiers across a range of frequencies. Biocal is not needed and usually not performed in digital recordings.

A routine EEG recording should be at least 20 minutes of artifact-free recording. At least two bipolar (longitudinal and transverse) and one referential montage should be used (essential for analog EEG equipment, but recommended for digital recordings). Because the effect of activity on the EEG is important for interpretation, activation techniques should also be included (such as eye opening and closure, photic stimulation, hyperventilation, or others).

## RECORDING MONTAGES

The EEG signal varies not only with time but also with location on the head. The data are recorded from multiple locations on the scalp. To accurately represent cerebral activity, the EEG must be displayed to show both the variation with time and with spatial location. The spatial variation in the EEG is typically conveyed by the orderly arrangement of electrode derivations, the montage. The voltage recorded from multiple scalp locations simultaneously is displayed by combining the signal from electrode pairs or combinations. At a basic level, this process filters the EEG signal across space. Just like frequency filtering can both accentuate activity of interest and distort the signal, montages can both highlight certain types of activity while distorting others. Thus, the signals must be interpreted in the context of the montage being used and montages should be selected to highlight the activity of interest. For example, a montage where the electrodes are arranged longitudinally (front to back) will preserve information about spatial relationships in the sagittal plane better than one where electrodes are arranged in a transverse direction (side to side).

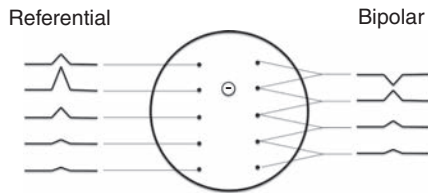
There are many types of montages. Montages may be classified in several ways (4) based on the relative arrangement of electrodes: unpaired, electroanatomical paired-group, or paired channel. In unpaired montages, channels

are arranged in anatomical neighboring sequence, for example, sequentially from front to back or left to right. An example is a longitudinal bipolar montage where electrodes are arranged in a sagittal plane (from left to right) with electrodes going from front to back. In paired-group montages, electrodes from corresponding areas are placed next to each other. These are always longitudinal: for example, left temporal electrodes placed adjacent to right temporal electrodes. In paired-channel montages, individual electrodes from the left and right hemispheres from corresponding areas are placed together. Paired-group and paired-channel montages are useful for highlighting asymmetries between the two hemispheres.

Montages can also be classified by the type of derivation: referential, bipolar, or Laplacian. In a referential montage, the voltage from each electrode is displayed with respect to a common electrode (the reference). Ideally, the reference electrode should be “inactive,” that is, not contain any of the activity of interest. In real life, this is not possible, so, instead the reference is selected to be relatively inactive. Commonly used references include A1 and A2 (ipsilateral or contralateral ear), A1+A2 (linked ear), Cz, balanced noncephalic (such as neck-chest region) and the average reference. The average reference is derived by averaging the voltage in all scalp electrodes. Sometimes, electrodes containing prominent artifacts or prominent cerebral activity are excluded from the calculation of the average reference. A carefully selected referential montage will clearly display the polarity and field distribution of the field being measured. The amplitude of the activity will reflect the actual amplitude of the potential (Figure 10.6). However, if the reference is contaminated (eg, a Cz reference during sleep), it will distort the activity being measured.

In bipolar montages, both inputs are connected to active recording electrodes. Bipolar montages link sequential pairs of electrodes to form chains in the longitudinal (sagittal), transverse (coronal), or circular (axial) directions. In these chains, a single electrode becomes common to two adjacent channels; for example, A-B, B-C, C-D. In such chains, the site of maximal voltage within a potential field becomes a point of phase reversal (Figure 10.6). The direction of the phase reversal depends on the polarity of the voltage (deflections coming together for a surface-negative peak and divergent for a surface-positive peak). Localization by phase reversal is only feasible if the bipolar montage fully encompasses the voltage peak. If the peak occurs at the end of a chain, for example, a spike located at O2, no phase reversal will be seen. If this is noticed during the actual data collection, another electrode can be added to the end of the chain (eg, O2') to allow detection of a phase reversal.

Referential montages are useful for highlighting activity that has a fairly broad spatial distribution. Bipolar montages are better suited for activity with a more restricted spatial distribution. It is important to keep in mind that the amplitude of activity in a bipolar montage only reflects the difference in that potential between adjacent electrodes, not the actual amplitude.



**FIGURE 10.6** A surface negative potential as recorded by a series of electrodes. On the left is a referential montage, where each electrode is connected to input 1 of the amplifier and a reference electrode (not shown) is connected to input 2. The electrode closest to the potentials shows the highest amplitude signal (upward deflection for a negative potential); on the right, a bipolar montage where the electrodes are connected in a chain to the amplifiers. In this case, the chain shows a phase reversal centered around the electrode closest to the potential.

In montages, electrodes are always arranged in an anterior-to-posterior sequence. For longitudinal montages, the chains proceed from front to back; for transverse montages, the chains are displayed in a front-to-back sequence. In the United States and Canada, “left-over-right” convention is typically used. For longitudinal montages (unpaired or paired), the left-sided electrodes are placed before the right-sided electrodes or electrode groups. For transverse montage, each chain proceeds from left to right.

Because different montages have their own advantages and disadvantages, EEG recording and interpretation usually require the use of multiple montages. For analog recording, where data cannot be reformatted after collection, it was necessary to record the data using a variety of montages. The ACNS recommends that a standard recording should include at minimum a longitudinal bipolar montage, a transverse bipolar montage, and a referential montage. Beyond these minimum requirements, ideally, a technologist should be actively evaluating the data as it is being collected and select montages that highlight activity of potential interest. With digital recording, where montages can be easily changed after collection, this process becomes somewhat less necessary; however, maneuvers like placing additional electrodes must still be performed by a trained technologist during data collection.

### EQUIPMENT FOR LONG-TERM EEG MONITORING

There are some special requirements for the equipment used for long-term EEG monitoring (LTM). First, because the main purpose of LTM is to record events/seizures and correlate the EEG with the clinical events, simultaneous video and audio recording that is synchronized with the EEG is required. In the past, complicated arrangements of analog EEG recording were combined with analog video and audio recording for this purpose. However, today, almost all LTM recordings, including the video and audio components, are digital.

For the EEG signal itself, the basic requirements are similar to routine EEG. However, LTM often requires the use of additional channels. This can include EEG data from additional locations on the scalp as well as include channels for electromyography (EMG) to record movement/muscle activity and even channels for recording respirations or oxygen saturation. Most machines include the capability of recording approximately 32 channels of EEG data, including several channels for DC-coupled recording for recording non-EEG signals. LTM systems should have a minimum sampling rate of 400 samples/sec/channel (to reasonably reproduce signals with a frequency of 100 Hz). Most modern systems have sampling rates above 1000 samples/sec/channel. The jack box is usually worn by the patient and is fairly lightweight. A cable connects the jack box to the base unit nearby. The length of the cable should be sufficient to allow the patient to move around the hospital rooms. Some systems have batteries and storage space built into the jack box. This allows the EEG to continue recording for several hours, even with the jack box disconnected from the base unit.

The video and audio recordings must be of sufficient quality to record subtle changes. For video, the recording must be able to record in low-light conditions (at night); this is usually accomplished using an infrared light source. Optimal recording usually requires that the video camera and microphone for audio recording be permanently mounted in the room. Portable systems, where the camera, infra-red light source, and microphone, which are mounted on a cart, can also be used for long-term monitoring. Dual-camera systems are sometimes used to provide a close-up and zoomed-out view of the patient. The cameras are usually networked and can be controlled (moved) remotely.

Intracranial recording requires special amplifiers. These amplifiers typically require far more channels (64 to 256 or more) with higher sampling rates (500 to >10,000 samples/channel/sec). The ability to connect an electrical stimulator to the intracranial electrodes is also required for brain mapping. Depending on the system, this process may be fully manual (requiring plugging electrodes to be stimulated directly into the stimulator) or fairly automated where the pair of electrodes to be stimulated is selected on the computer.

### EQUIPMENT FOR ICU EEG MONITORING

The requirements for ICU EEG monitoring are similar to LTM in most cases. Simultaneous recording of video and audio is still desirable. Additional electrodes are less commonly used. The systems may be hard-wired into the ICU rooms (ie, cameras and base units permanently mounted on the units) or, more commonly, may be a portable unit mounted on a cart. Hard-wired units have the advantage of optimized placement of cameras, microphones, and the equipment to avoid interference with other equipment and personnel. However, they lack the flexibility of a portable machine that can be wheeled to wherever it is needed.

In most cases, the electrodes used are similar to those used for routine recordings. However, the advantages of using disposable and/or CT/MRI-compatible electrodes are often a bigger issue due to the higher infection risks and more frequent need for imaging studies in these patients. Subdermal needle electrodes are more commonly used in these patients due to ease of application.

Remote access to the data being collected is a crucial issue for ICU EEG monitoring. Because these recordings need to be reviewed frequently and likely at unusual times of the day, it is important that the data be available to the neurophysiologist by remote access from both within and outside the hospital. Finally, quantitative EEG tools are usually a desirable feature of the software. Quantitative EEG trends are a useful tool for reviewing the vast amounts of data produced in ICU EEG monitoring.

It is important to have an understanding of the generators of EEG waveforms. The EEG signal is complex and

its recording has to be performed with a standardized technique. Having an understanding of the limitations of the EEG recording device and how to improve recorded signals facilitates proper interpretation.

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# Normal EEG

*Aatif M. Husain*

A clear understanding of a normal EEG is mandatory before studying abnormalities. Recognizing variations of a normal tracing can be challenging. Interpreting rhythmic or sharply contoured normal discharges as abnormal and epileptiform can lead to the erroneous diagnosis of epilepsy and years of unnecessary treatment (1,2). “Overreading” EEG is more common than “underreading,” and can lead to more patient distress (3,4).

Features of a normal EEG will be presented in this chapter. Normal patterns seen during wakefulness and sleep will be presented first. This will be followed by a discussion of normal changes seen during activation procedures. Normal variants of EEG will be presented thereafter, and finally a discussion of artifacts will follow. Where relevant, changes seen in children and the elderly will be discussed. Normal patterns commonly misinterpreted as epileptiform will be specifically noted, and clues to differentiate the two will be presented. For additional details, the reader is referred to excellent texts and atlases on this subject (5–8).

## NORMAL AWAKE EEG

There are many features of a normal awake EEG that should be sought in every recording. Not all features will be seen in each EEG. These features are discussed further.

### Alpha Rhythm

The alpha rhythm is the predominant activity noted in the occipital region during relaxed wakefulness. Alpha rhythm is distinct from alpha frequency; the latter denotes EEG activity between 8 and 13 Hz. Alpha rhythm is the name applied to a particular type of alpha frequency activity that occurs in a normal awake individual and has certain characteristics.

As the name implies, alpha rhythm has activity ranging from 8 to 13 Hz (alpha frequency). The frequency is the same in both hemispheres and remains constant during the recording, except for two situations. During drowsiness, it may slow by 1 Hz, and immediately after

eye closure, it may be a little faster. The latter is known as alpha squeak (Figure 11.1). Normal individuals, even the elderly, should have an alpha rhythm that is at least 8.5 Hz. Only 1% of normal individuals will have a slower frequency, so when it is seen, abnormality should be suspected (9).

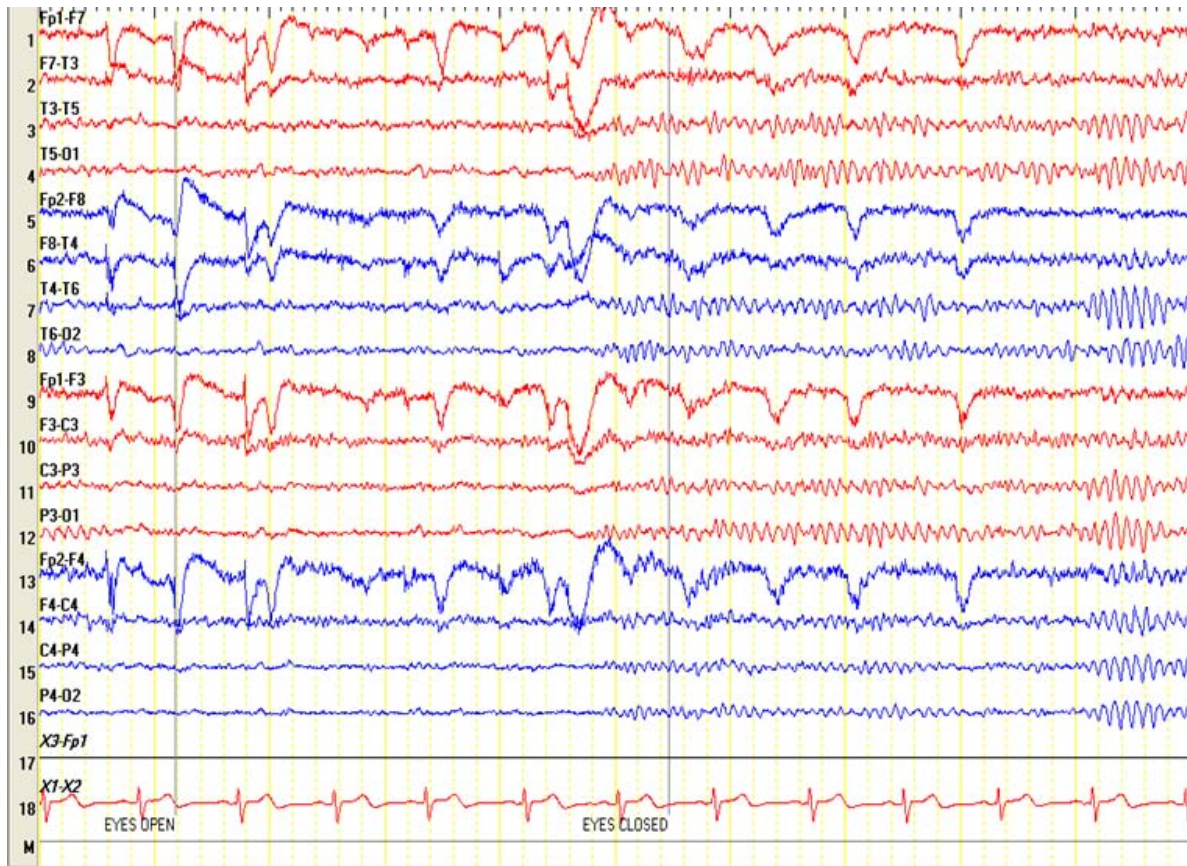
Alpha activity is of highest amplitude in the occipital region. It may project to central and temporal regions, particularly in children and young adults. In an ear, reference montage frontal leads may show alpha rhythm as well due to contamination of the reference (ear) with the alpha activity.

The morphology of the alpha rhythm is usually sinusoidal and regular. It may appear peaked at the top or bottom of the waveform if there are superimposed beta frequencies; this is referred to as apiculate alpha activity (10) (Figure 11.2). Apiculate alpha activity can be differentiated from sharp waves by its association with similarly shaped waveforms (ie, “does not disrupt the background”), location, disappearance during sleep, and absence of an aftergoing slow wave.

Amplitude of the alpha activity varies during the tracing and between the hemispheres. More often the amplitude on the right side is higher; unless the amplitude on the left side is less than 50% of that on the right, it should not be considered abnormal. Amplitude differences occur because of the thickness of the occipital bone (7). Amplitude asymmetries are best assessed in an ear reference montage. Waxing and waning of the amplitude can also occur when two frequencies (ie, 10 and 11 Hz) occur together. This is referred to as “beating” of the alpha activity.

Reactivity is another important feature of alpha activity. Alpha activity is seen in relaxed wakefulness with eyes closed. The disappearance, or blocking, of the alpha activity with eye opening, stimulation, or even mental concentration is known as reactivity. Blocking of the alpha activity should occur simultaneously in both hemispheres; if it occurs only on one side, the other is abnormal. This is called Bancaud phenomenon. In some patients, alpha activity disappears with eye closure but appears with eye opening. This is known as paradoxical alpha rhythm. This does not have a





**FIGURE 11.1** Alpha rhythm with a 10 Hz background. Notice blocking with eye opening and closure. Immediately after eye closure, the alpha rhythm is 11 Hz (alpha squeak).

pathological significance. Reactivity of the alpha activity should be tested in every patient with eye opening and closing or with other types of stimulation.

Alpha rhythm is more appropriately referred to as posterior dominant rhythm in young children as the frequency of this activity is less than alpha frequency. Between term and 3 months, a clear posterior dominant rhythm is not present. After 3 months, an anterior-to-posterior gradient appears, and the posterior dominant rhythm frequency is about 3.5 to 4 Hz. It is 4 Hz by 6 months, 6 Hz at 12 months, and 7 Hz at 18 months. At 2 years, the posterior dominant background is 8 Hz and increases to 9 Hz by 7 years. By late childhood (around 10 years), it reaches 10 Hz (Table 11.1). In older children and adolescents, high-amplitude delta waves often interrupt the posterior dominant rhythm. These posterior slow waves of youth consist of delta waves with overriding alpha activity. The delta waves and the overriding activity are reactive to eye opening and stimulation (11,12).

In the elderly, the frequency of the alpha activity slows slightly, from 10–11 Hz to 8.5–9 Hz. However, as noted earlier, a frequency of 8 Hz, even in this age group, is considered abnormal. The distribution of the alpha activity also moves more anteriorly, and is often noted more in the frontocentral regions. The persistence and voltage also decrease with age.

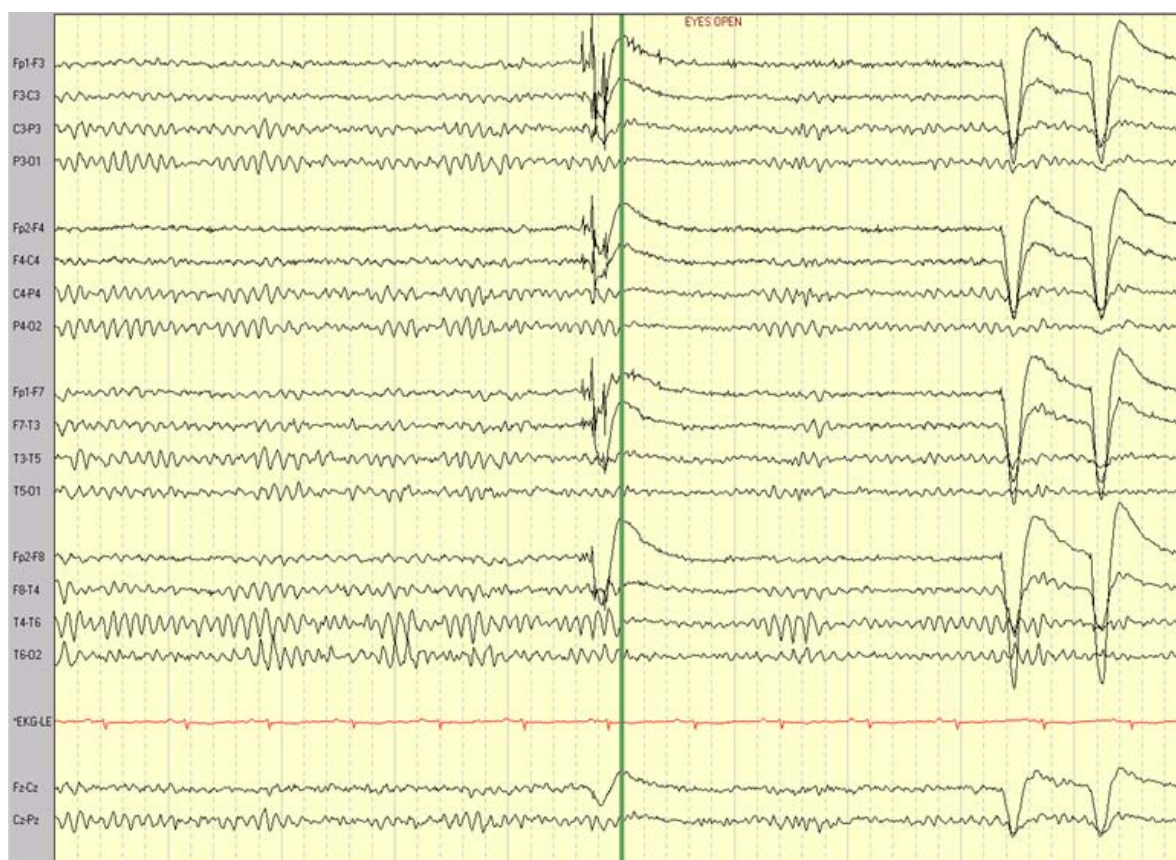
All these characteristics of the alpha activity should be noted. However, the absence of alpha activity is not an abnormality. A number of adults may not have an alpha rhythm; instead, their occipital rhythm is a low-amplitude activity, which will be discussed later.

### Beta Activity

Beta activity is EEG activity that is greater than 13 Hz. Unlike alpha rhythm, beta activity is defined only by its frequency. Most beta activity is between 15 and 25 Hz. It commonly occurs in the frontal and central regions in awake individuals (Figure 11.3). Unilateral attenuation of this activity can be seen with movement of the contralateral limb. Beta activity is usually of low amplitude, often less than 20  $\mu$ V.

Widespread beta activity may also be seen in some individuals and may be a medication effect (Figure 11.4). Benzodiazepines, barbiturates, and other sedatives cause an increase in the amplitude of beta activity, thus making it more prominent. Beta activity persists in light sleep and rapid eye movement (REM) sleep, but is less common in slow wave sleep. A particular type of beta activity, fast alpha variant, is noted in the occipital region and is discussed with normal variants.





**FIGURE 11.2** Temporal and central spread of the alpha rhythm. Notice the apiculate alpha in the 2nd second.

**TABLE 11.1** Posterior Dominant Rhythm in Pediatrics

AGE	POSTERIOR DOMINANT RHYTHM
Term to 3 months	Not clearly present
3 months	3.5–4 Hz
6 months	4 Hz
12 months	6 Hz
18 months	7 Hz
2 years	8 Hz
7 years	9 Hz
10 years	10 Hz

With age, beta activity tends to increase, as does its amplitude. As individuals become very old, the beta activity may decrease. This change is also associated with cerebral atrophy; consequently, the loss of beta activity in very old age may represent pathology rather than normal aging (7).

### Theta Activity

Theta activity includes frequencies between 4 and 7 Hz. Though it is frequently abnormal, occasionally theta activity

can be normal. Theta activity in the 6–7 Hz range can be seen in wakefulness in the frontocentral area in young individuals. This activity is present in states of heightened attention or vigilance (9,13). As the individual falls asleep, this activity disappears.

Temporal theta activity may be seen in individuals older than 60 years. This activity can occur as a single wave or in brief runs. It is seen on both sides, though it is more often seen over the left hemisphere. In between bursts of temporal theta activity, alpha rhythm may be seen. Like the alpha rhythm, temporal theta activity is reactive to eye opening and stimulation. Such intermittent temporal theta activity is normal; however, it is abnormal when it is persistent and of high amplitude (14).

Another type of theta activity, known as the slow alpha variant, will be discussed with normal variants. High-amplitude theta activity can also occur with hyperventilation, and this will be discussed later as well.

### Delta Activity

Delta frequencies are less than 4 Hz. They are less common than theta frequencies in the normal awake adult EEG. When present, they occur only in the elderly in the same distribution as temporal theta activity. These delta waves should be of the same amplitude as the alpha rhythm, occur as single



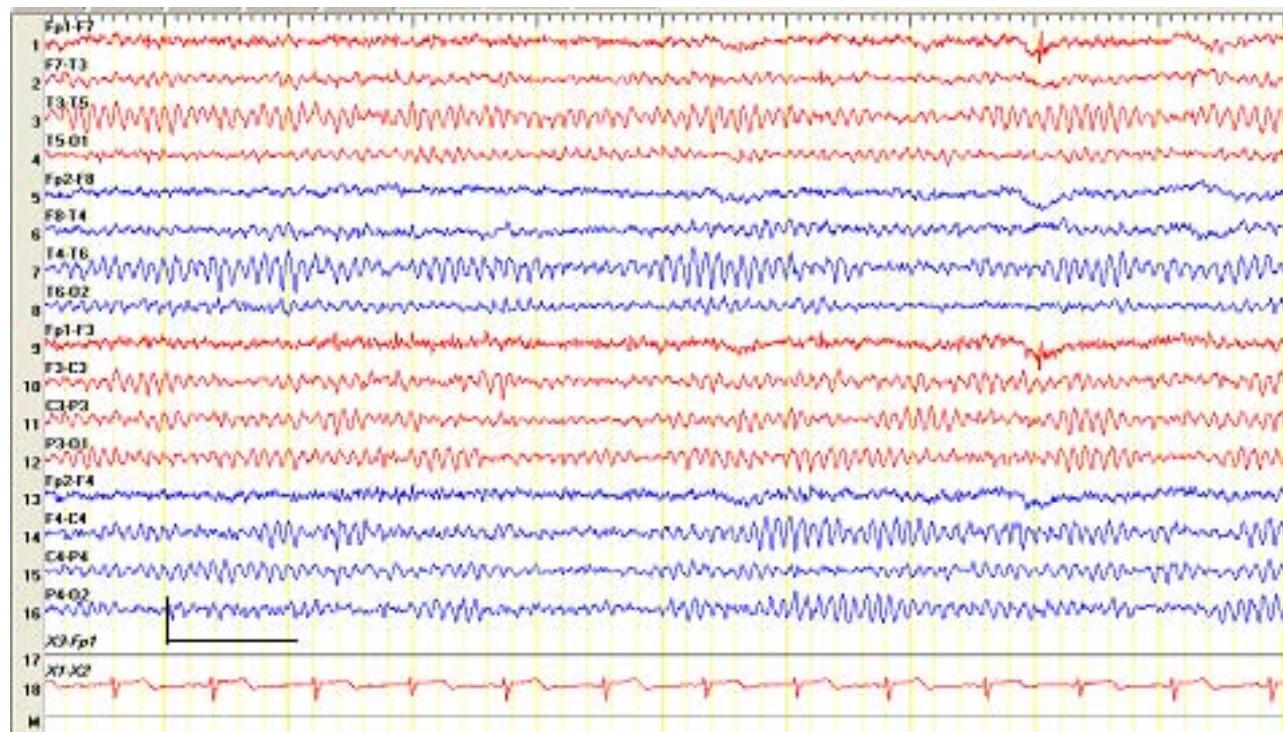


FIGURE 11.3 Beta activity is present in the frontal regions bilaterally. This activity is about 20 Hz and less than 20  $\mu$ V.

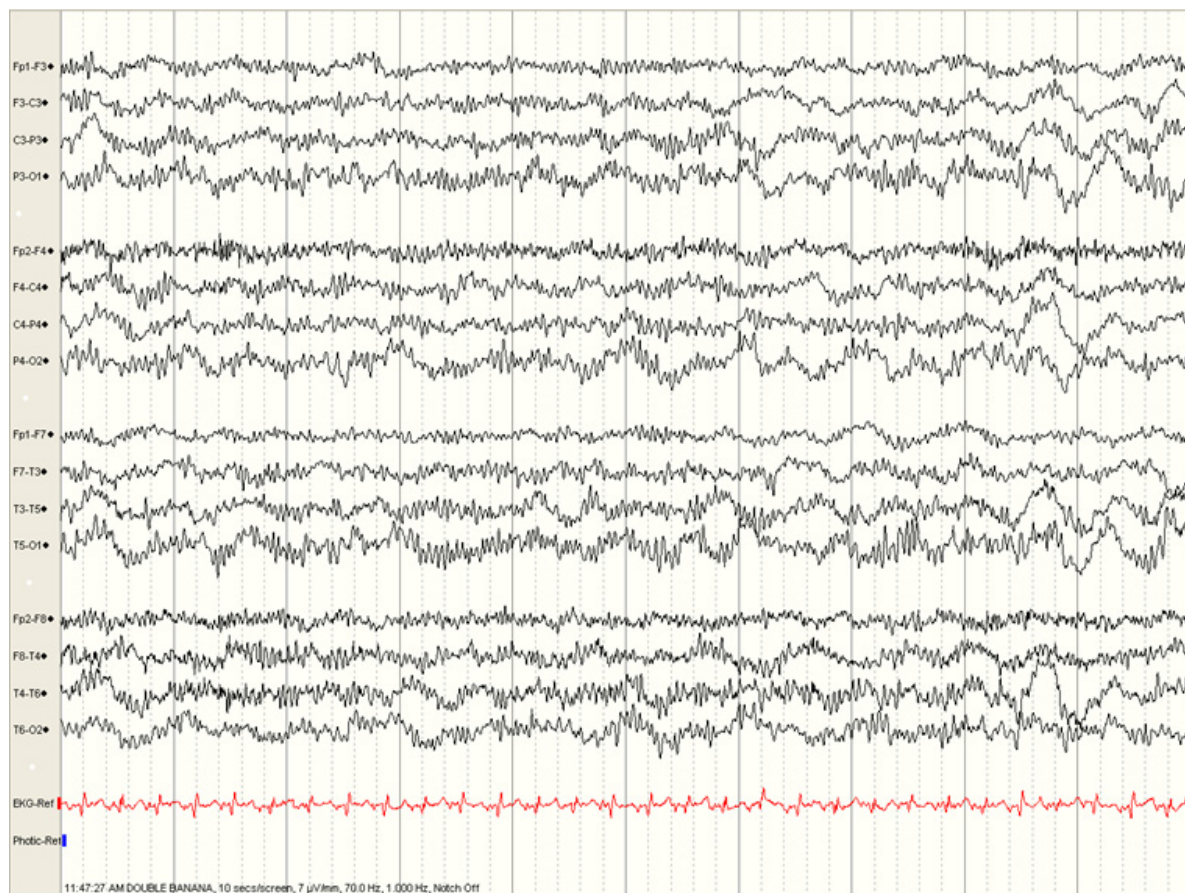


FIGURE 11.4 Widespread beta activity due to lorazepam use.



waves, and occupy less than 1% of the record (15). If delta waves are more frequent or of a higher amplitude, they represent an abnormality. It should be remembered, however, that delta frequencies are commonly seen in a normal sleep EEG (discussed later).

### Mu Rhythm

Mu rhythm is an arch-shaped activity seen over the central or centroparietal regions. Its frequency is similar to alpha rhythm, 8–11 Hz. Mu rhythm is asymmetric and asynchronous over the two hemispheres and is frequently interspersed with beta activity (Figure 11.5). Mu activity blocks when the individual is asked to move the contralateral extremity. Paradoxical mu rhythm is when this activity appears with contralateral limb movement. At times, the apiculate phase of the mu rhythm can resemble spikes, particularly when there is an overlying skull defect. The lack of an aftergoing slow wave, typical location, and reactivity can help differentiate benign mu activity from central spikes. Mu activity is seen more commonly in younger individuals and decreases with age.

### Lambda Waves

Lambda waves are saw tooth-shaped waveforms of positive polarity seen in the occipital region. They are usually between

160 and 250 ms in duration and less than 50  $\mu$ V in amplitude. Lambda waves are usually bilaterally synchronous, though they can occur asymmetrically and mimic sharp waves. They occur when an individual is scanning a complex visual image and can be eliminated when asked to look at a blank white sheet of paper (10). As they are best seen with visual scanning, eye blink artifact is often seen with lambda waves (Figure 11.6). These waves are most often seen in younger individuals, and they decrease in the elderly.

### Low-Voltage EEG

In some individuals, a clear alpha rhythm cannot be identified. Instead, their background activity is a low-amplitude activity with beta, alpha, and theta frequencies. The amplitude of this activity is usually less than 20  $\mu$ V (Figure 11.7). A low-voltage EEG is seen more often in older individuals than in children and is not considered an abnormality unless a previous EEG in the same patient showed clear alpha rhythm. When all activity is less than 10  $\mu$ V it may be abnormal.

### NORMAL SLEEP EEG

There are several characteristic EEG waveforms that occur in sleep. They occur in different stages of sleep, and their presence or absence helps determine the sleep stage. These



FIGURE 11.5 Mu activity occurring asymmetrically over the central regions.

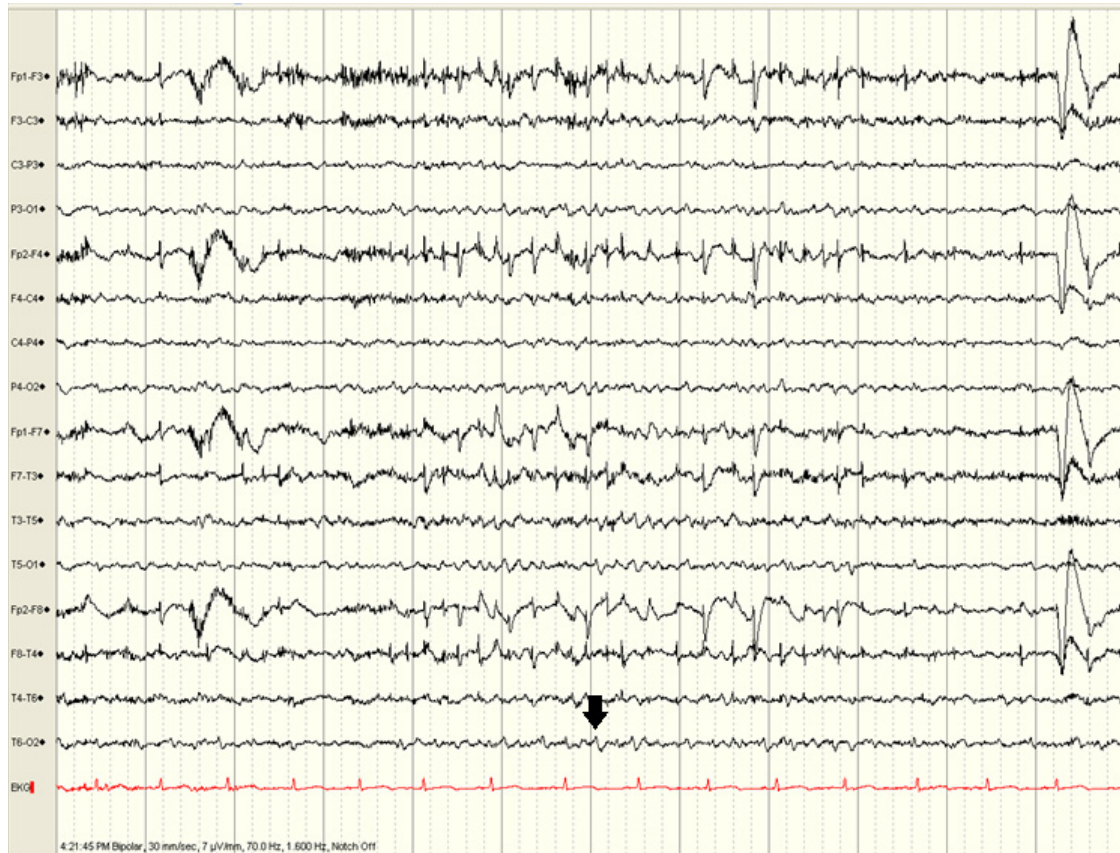


FIGURE 11.6 Triangle-shaped lambda waves occurring synchronously in occipital regions (arrow).

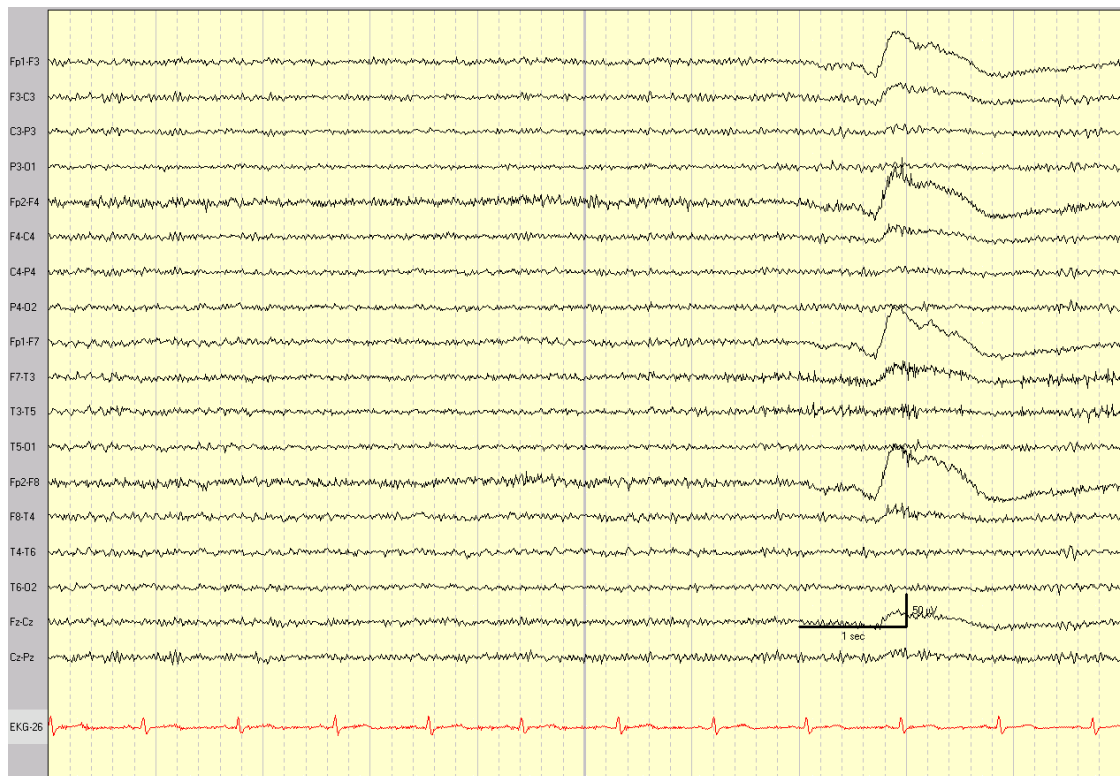


FIGURE 11.7 A low-voltage, mixed-frequency EEG, without clear alpha rhythm.



waveforms will be discussed first, and then features of the various sleep stages will be presented.

### Vertex Waves

Vertex waves, also called V waves, are surface-negative, biphasic discharges that are of maximal amplitude over Cz (vertex, hence their name). They can project to Fz and Pz, as well as to parasagittal frontal and central electrodes. A phase reversal over Cz is seen in a transverse bipolar montage, which is best for identifying sleep architecture (Figure 11.8). Vertex waves decrease in amplitude with age, and in young children these waves may be of high amplitude and phase reverse over Fz. Occasionally, they can be asymmetric and resemble central spikes. Persistent asymmetry should raise suspicion of an abnormality. Vertex waves can occur in runs or with other sleep architecture. They are mostly seen in light stages of sleep (stage I) but can occur with deeper stages as well. Rarely low-amplitude vertex waves may be seen in awake individuals. A loud noise or an alerting stimulus can induce vertex waves in a sleeping individual.

### Positive Occipital Sharp Transients of Sleep

Positive occipital sharp transients of sleep (POSTS) are monophasic, triangular waveforms of positive polarity.

They are common and are seen in most normal individuals. As their name implies, POSTS are seen in the occipital region during light sleep. They often occur synchronously but can occur independently. POSTS usually recur at an irregular frequency; however, they can occur in trains of about 1 per second. Morphologically, they resemble lambda waves, and when they are of high amplitude, they can mimic sharp waves (Figure 11.9). Their monophasic morphology, location, and occurrence only in light sleep differentiate them from epileptic sharp waves.

### Sleep Spindles

Sleep spindles are a series of rhythmic waves occurring at a frequency of 12 to 14 Hz and lasting at least 0.5 second. They are best seen over the vertex, but have a wide distribution. In adults, sleep spindles are symmetric and synchronous (Figure 11.10). They are a hallmark of stage II sleep, but can be seen in deeper stages. In deeper stages of sleep, sleep spindles occur at a slightly slower frequency and are more prominent over Fz.

### K Complex

A K complex is a biphasic with an initial sharp component, followed by a slow wave. Its distribution is similar to that



FIGURE 11.8 Vertex wave seen over the vertex in a transverse montage.



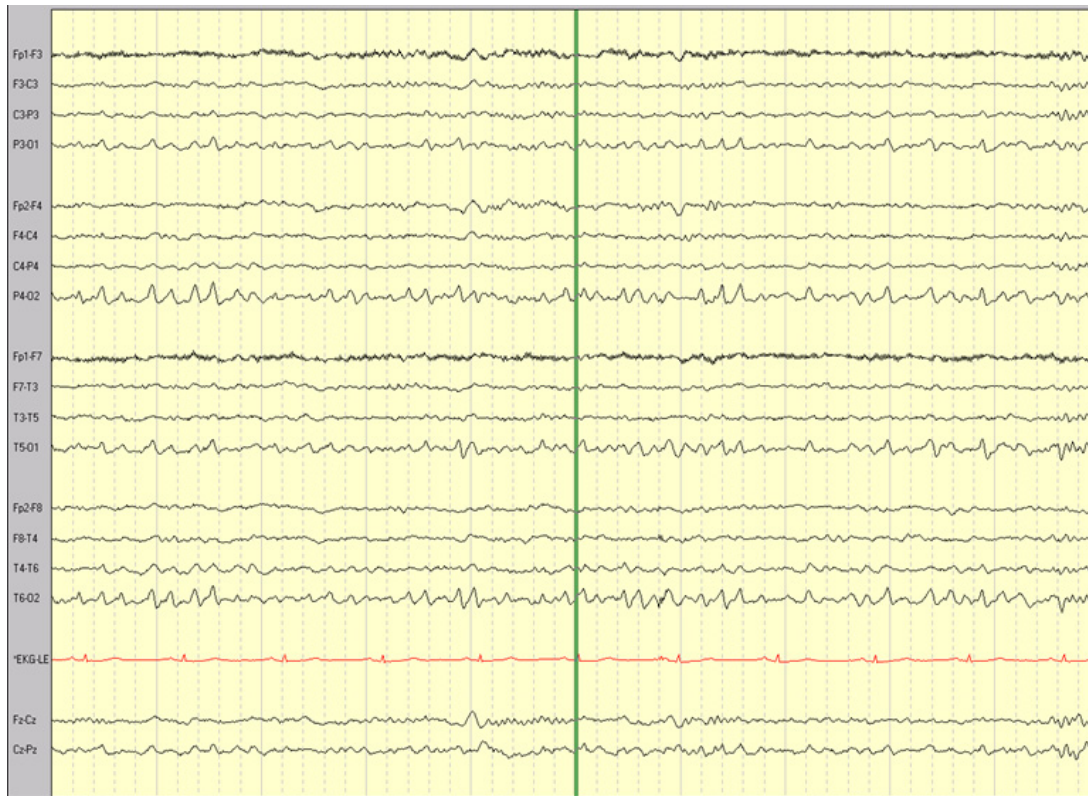


FIGURE 11.9 POSTS are seen synchronously in the posterior regions.



FIGURE 11.10 Sleep spindles (short arrow) and K complex (long arrow) are seen on this page. They are seen best over the vertex in a transverse bipolar montage.

of vertex waves. Sleep spindles usually follow the slow wave of a K complex (Figure 11.10). They are seen in stage II sleep and auditory stimuli can induce K complexes in a sleeping individual. It should be noted that although there is an amplitude criteria for K complexes in polysomnography, similar criteria do not apply in EEG.

### Delta Waves

Though all EEG frequencies less than 4 Hz are considered delta, delta waves in sleep are waves that are 2 Hz or less in frequency and have an amplitude of at least 75  $\mu$ V. Delta waves are widespread and symmetric, though not necessarily synchronous. They are seen in deep sleep (stages III and IV) and often with other types of sleep architecture, such as sleep spindles. The abundance of delta waves decreases in old age.

### Rapid Eye Movements

REMs are not an EEG waveform, rather they are a useful biologic artifact. Eye movement artifact is seen most prominently in the frontal region. REM are differentiated from slower eye movements by the upslope of the deflection,

which is less than 300 ms (16) (Figure 11.11). REMs are usually lateral eye movements. Lateral eye movements will show out-of-phase deflections in the temporal chain (F7, F8) of an anterior posterior bipolar (double banana) montage. REMs are seen in wakefulness as well as REM sleep.

### Slow Eye Movements

Slow eye movements (SEM) are differentiated from REM by an upslope that is greater than 500 ms. The distribution of SEM is similar to that of REM. SEM, however, are seen in drowsiness and light sleep, and they disappear in deeper stages of sleep.

### Sleep Stage I

The lightest sleep is stage I, also referred to as stage non-REM 1 (N-1). In early stage I, or drowsiness, there is slowing of the alpha rhythms, persistence of frontocentral beta frequencies, and appearance of SEM. Once the alpha rhythm disappears, the EEG consists of low-amplitude, mixed-frequency activity. Vertex waves and POSTS also appear in this stage. Stage I is a short-lived stage, often quickly transitioning to stage II.

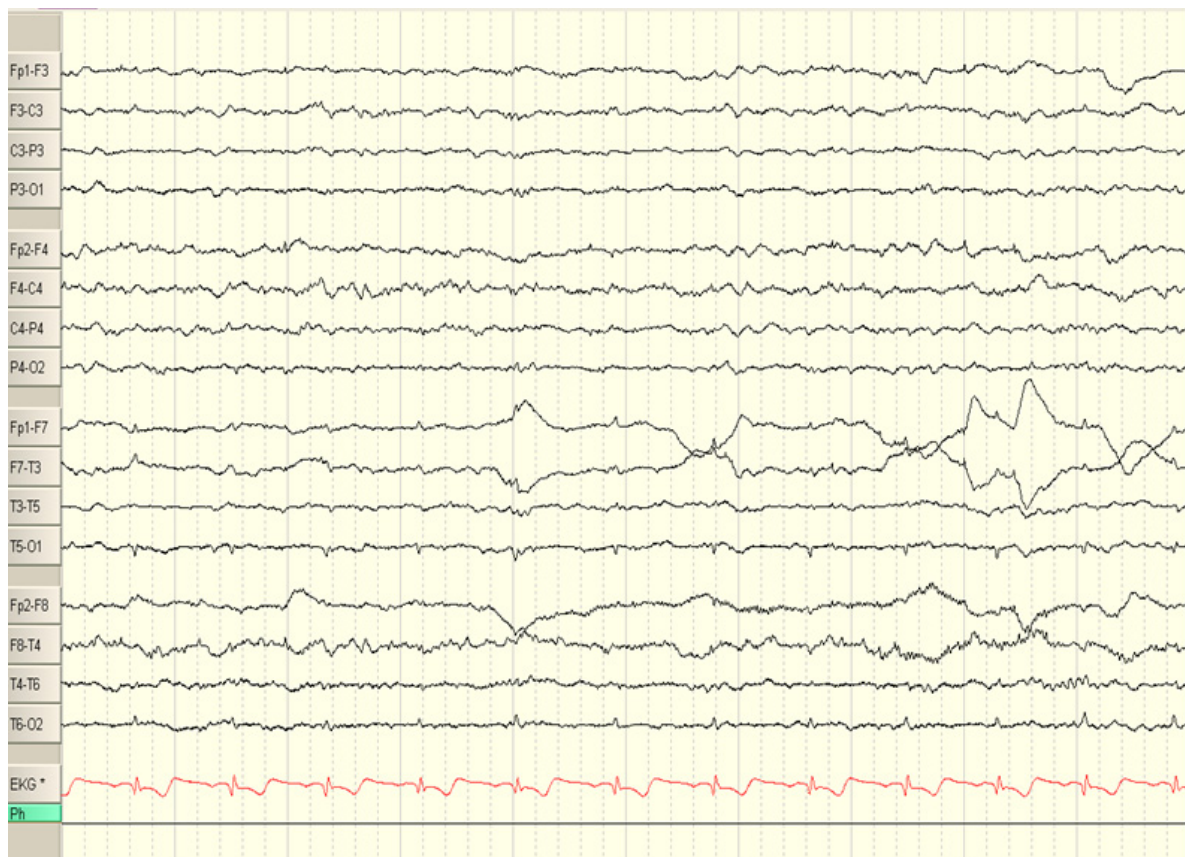


FIGURE 11.11 REM noted best in Fp1/Fp2 – F7/F8 channels.



### Sleep Stage II

Stage II sleep is the most abundant sleep stage, also referred to as stage N-2. It is characterized by sleep spindles and K complexes. Vertex waves and POSTS can persist in stage II. Waves of 3–7 Hz frequency are also seen; however, delta waves (as described earlier) are uncommon in stage II.

### Sleep Stage III

Stage III is characterized by delta waves occupying more than 20% of the recording time. This stage is also referred to as stage N-3. Sleep spindles and K complexes are also often present, POSTS can sometimes be seen, and vertex waves are uncommon. Stage IV is similar to stage III, except that delta waves occupy greater than 50% of the recording. Stages III and IV are not usually seen in a routine EEG.

### Sleep Stage REM

The EEG in stage REM consists of low-amplitude, mixed frequencies, similar to that seen in stage I. REMs are the hallmark of this stage. Saw tooth waves, which are a run of vertex waves, are seen often; however, isolated vertex waves are rare. Electromyographic (EMG) artifact is not seen as there is muscle atonia in REM sleep. Because stage REM usually does not occur until about 90 minutes after sleep onset, it is unusual to see it in a routine EEG. If it is seen, the individual may be sleep deprived or may have a disorder of REM regulation.

### Sleep in Children

Sleep architecture changes rapidly from early infancy to adolescence. Between the age of term and 3 months, when the child falls asleep, the first stage of sleep is often stage REM, also known as active sleep at this age. After 3 months of age, stage I becomes the first stage of sleep. Sleep spindles and vertex waves appear before the age of 3 months. By 6 months, vertex waves are prominent, as are sleep spindles. The latter, however, are asynchronous but symmetric. Often the spindles can be prolonged, lasting up to 10 seconds. Central theta waves appear by 6 months as well. Cone waves, high-amplitude posteriorly dominant delta waves, can be seen asynchronously in sleep as well.

As the child grows older, slow-wave activity during sleep becomes more prominent. After the age of 12 months, there is marked increase of delta activity during drowsiness. Between 12 and 24 months, K complexes appear. Sleep spindles gradually become more synchronous, and by 24 months they are fully synchronous. Vertex waves are most prominent over the central head regions. At times, these can resemble spikes, but it is important to differentiate them from epileptiform activity. Sleep spindles, vertex waves, and K complexes are frontocentrally located in this age group.

Beyond the second year of life, the sleep architecture starts to resemble that in adults. Differences remain in the

quantity of various sleep stages. The total amount of REMs and stage 3 sleep gradually decreases with age, while stage 2 increases.

### Sleep in the Elderly

With increasing age, sleep-onset latency becomes longer. This makes it less likely to record sleep in a routine EEG in the elderly. The amount of stages I and II sleep increases, while stage III decreases to less than 10% of the total sleep time. REM sleep also decreases to less than 20% by age 70 years.

## ACTIVATION PROCEDURES

Three activation procedures are commonly used in routine EEG: hyperventilation, photic stimulation, and sleep. Normal sleep EEG has been discussed already, and changes with hyperventilation and photic stimulation will be presented in this section.

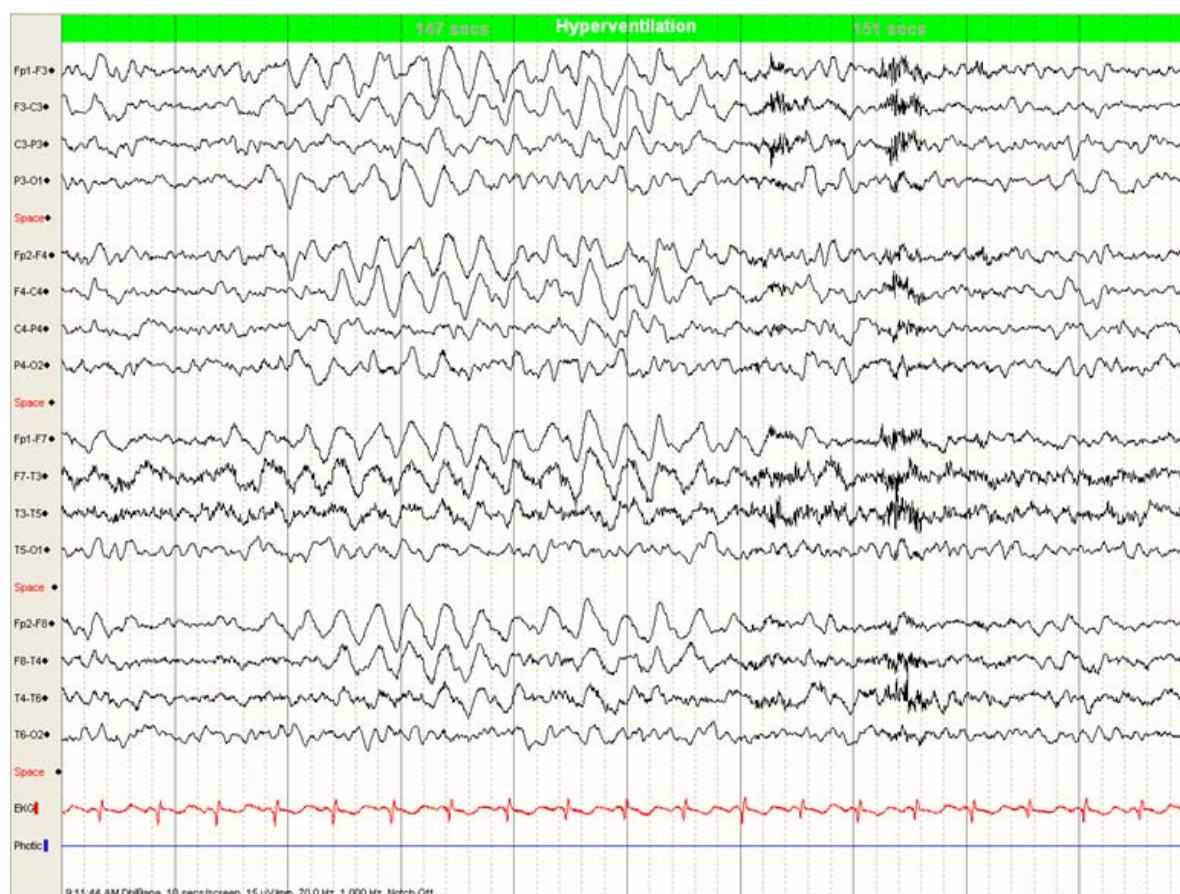
### Hyperventilation

Hyperventilation for 3 to 5 minutes is commonly performed in EEG laboratories. Hypocarbica induced by hyperventilation and the resulting cerebral vasoconstriction and hypoperfusion is thought to be responsible for the changes that occur. A normal response consists of gradually increasing theta frequencies, followed by rhythmic delta bursts, and finally generalized, continuous, rhythmic delta activity. This activity is initially noted in the frontal region in adolescents and adults (Figure 11.12). Sixty to ninety seconds after stopping hyperventilation, the slow activity begins to subside. Hyperventilation-induced slowing is more prominent if the individual's blood sugar is low (long time since last meal) or if significant cerebral ischemia occurs. It is much more remarkable in younger patients and is difficult to elicit in the elderly.

Abnormal responses to hyperventilation include generalized spike and wave discharges, focal spikes, or lateralized slowing. Lateralized slowing may be more evident in the posthyperventilation period when the generalized delta activity is subsiding. If epileptiform discharges or focal slowing is not seen, a hyperventilation response should be considered normal, even if it induces remarkable rhythmic delta slowing. Because it induces hypocarbica and cerebral vasoconstriction, hyperventilation should not be performed in patients with significant cardiopulmonary disease, acute stroke, sickle cell disease, or pregnancy.

### Photic Stimulation

Photic stimulation consists of brief bursts of light applied at frequencies of 1 to 30 Hz. The light produces a visual evoked potential that can be recorded best in the occipital area. At frequencies close to an individual's alpha rhythm, each flash evokes a time-locked response. This is known as



**FIGURE 11.12** A normal hyperventilation response with frontally dominant slowing.

photic driving. Photic driving can also occur at subharmonic or harmonic frequencies of the stimulus (Figure 11.13). The probability that such a driving response will be seen can be increased when the eyes are closed and the stimulator is less than 30 cm from the patient. The amplitude of photic driving can be different on the two sides; even an amplitude asymmetry of 50% is not abnormal (7). Another type of normal response to photic stimulation is a photomyoclonic response. This consists of contractions of the frontalis or periocular muscles at the same frequency as the stimulus. The artifact created by muscle twitching is noted in the frontal leads 50 to 60 ms after the stimulus.

A photoparoxysmal response is the most well-known abnormal response to photic stimulation. It consists of spikes and sharp waves that occasionally lead to a convulsive seizure. Though generalized discharges are most common, focal epileptiform abnormalities can also be noted (17). Asymmetric photic driving can also be abnormal, with the side not showing a driving response being abnormal.

### NORMAL VARIANTS

There are a number of rhythmic discharges and sharply contoured waveforms that were historically thought to be

associated with epilepsy, headaches, and psychopathology but are now considered to be benign variations of normal.

### Rhythmic Temporal Theta Bursts of Drowsiness

Rhythmic temporal theta bursts of drowsiness (RTTBD) were previously referred to as psychomotor variant and rhythmic midtemporal discharges (RMTD). As the name implies, this pattern consists of 5 to 7 Hz discharge in the temporal regions that occurs during relaxed wakefulness or drowsiness. The theta waves have a flat-topped, sharp, or notched appearance (Figure 11.14). RTTBD occur bilaterally or independently over the two hemispheres and are seen mostly in adolescents and young adults. The discharge is monomorphic and does not evolve in frequency, differentiating it from a seizure discharge. This resemblance with a temporal lobe seizure discharge was why it was initially called psychomotor variant. It is no longer considered to have clinical significance and is seen in approximately 2% of normal adults (18).

### Midline Theta Rhythm

Midline theta rhythm is a 4 to 7 Hz discharge seen most prominently over Cz but also spreading to parasagittal



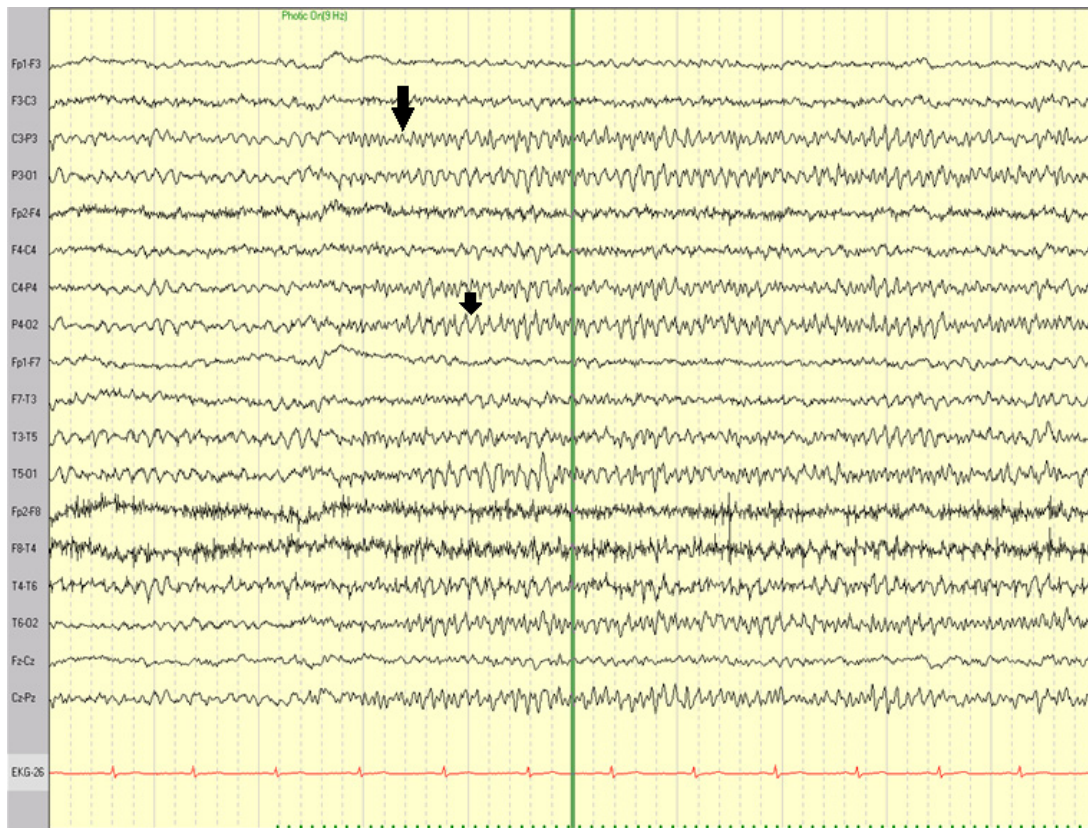


FIGURE 11.13 Normal photic driving at 9 Hz (short arrow) and harmonic driving at 18 Hz (long arrow).

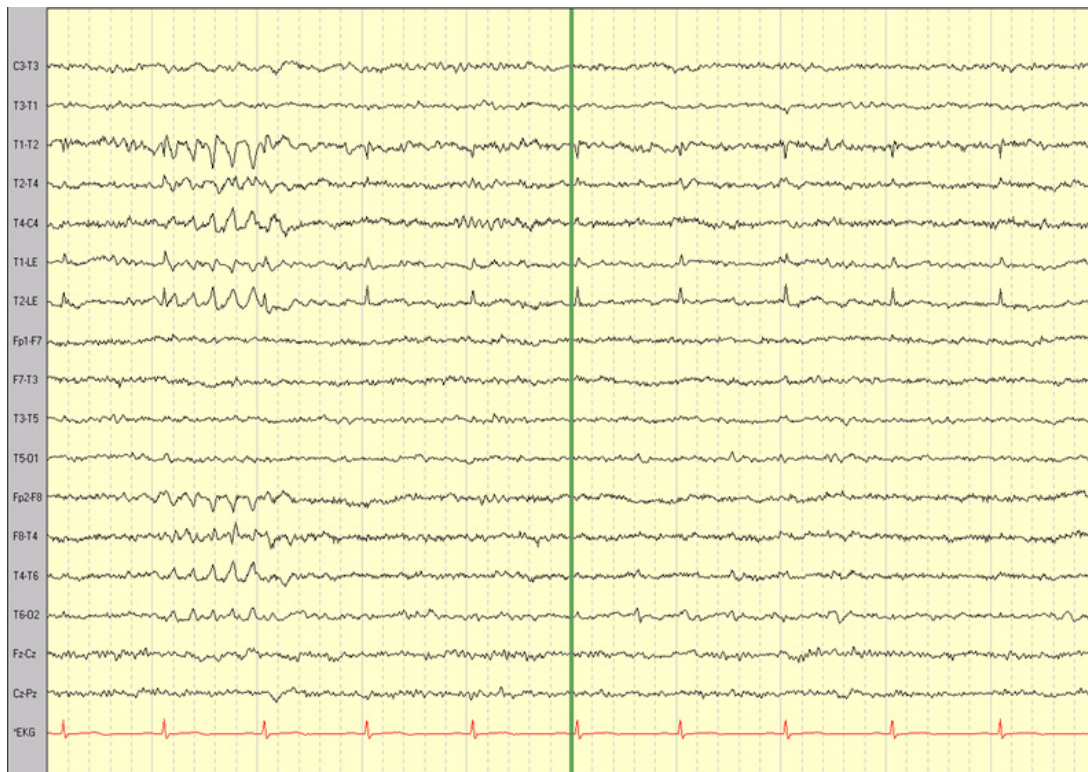
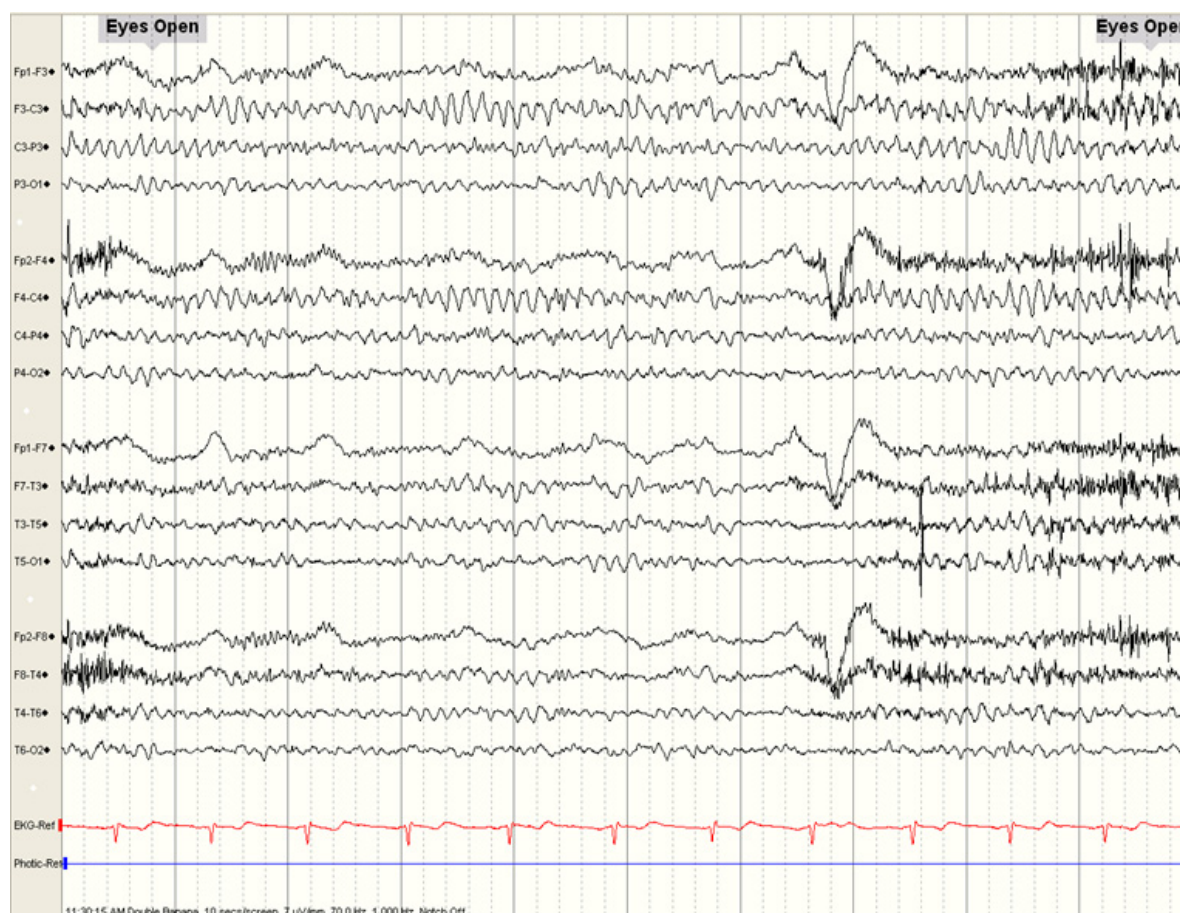


FIGURE 11.14 Sharply contoured rhythmic right temporal theta burst of drowsiness.



**FIGURE 11.15** Midline theta rhythm seen best over C3/C4 electrodes; notice lack of reactivity to eye opening.

leads. The discharge can have an archiform, sinusoidal, or mu-like appearance. It has variable reactivity to eye opening and limb movement (Figure 11.15). Like RTTBD, this rhythm is seen in relaxed wakefulness and drowsiness. When originally described, midline theta rhythm was thought to be associated with epilepsy, though now it is considered a normal variant (10).

### Alpha Variants

A number of variants of the alpha rhythm have been described. All have the same distribution and reactivity as normal alpha rhythm and often occur admixed with it. The slow alpha variant has a frequency of 4 to 5 Hz and can have a notched appearance (Figure 11.16). The fast alpha variant occurs at a harmonic of the underlying alpha rhythm, usually 16 to 20 Hz (Figure 11.17). Both slow and fast alpha variants are normal physiologic rhythms.

### Subclinical Rhythmic Electrographic Discharge in Adults

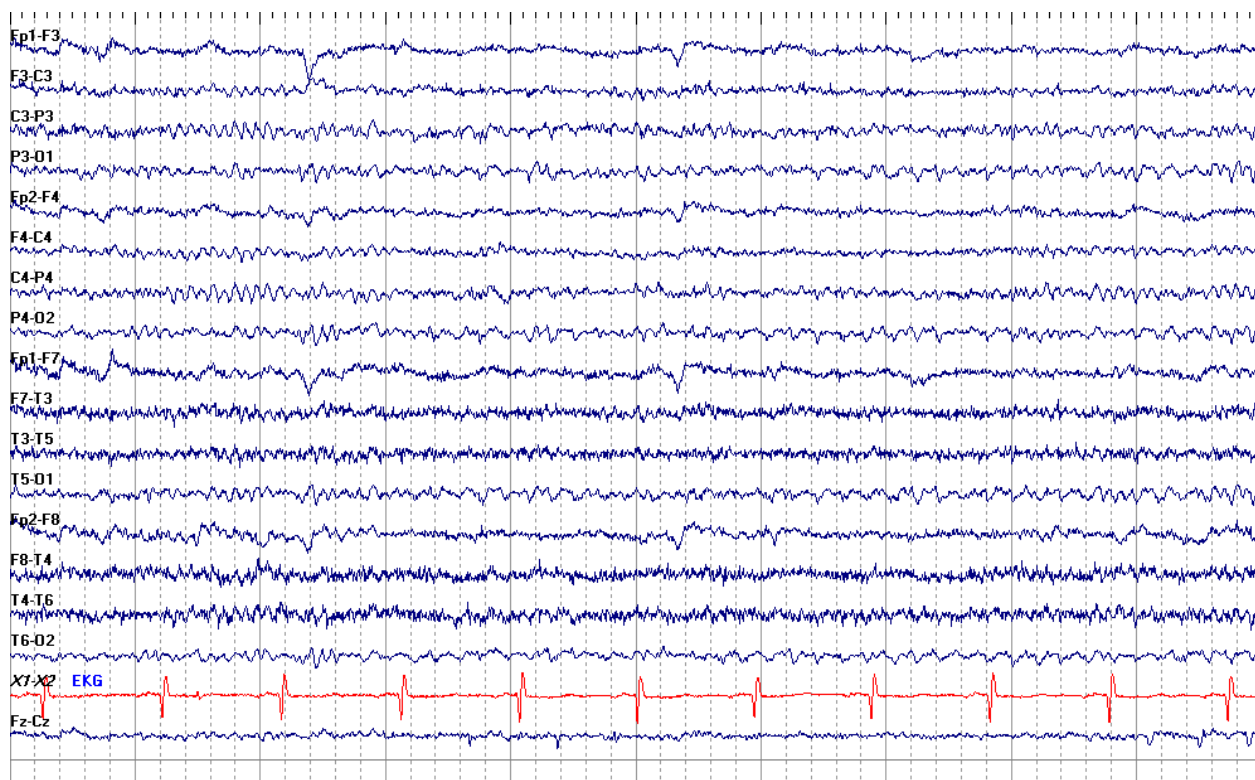
Subclinical rhythmic electrographic discharge in adults (SREDA) is an uncommon discharge seen mostly in older

adults. It occurs in relaxed wakefulness or drowsiness and consists of rhythmic theta and delta waves that evolve in frequency. Usually, it is a generalized pattern but can be more prominent focally. The usual duration is 20 to 40 seconds, but it can last several minutes. The onset of an SREDA pattern is either with a run of monomorphic sharp waves or high amplitude delta waves that suddenly interrupt the background (Figures 11.18A and 18B). Though this pattern resembles a seizure discharge, there is no alteration of consciousness or changes in cerebral blood flow (19). Consequently, SREDA is considered a benign EEG phenomenon.

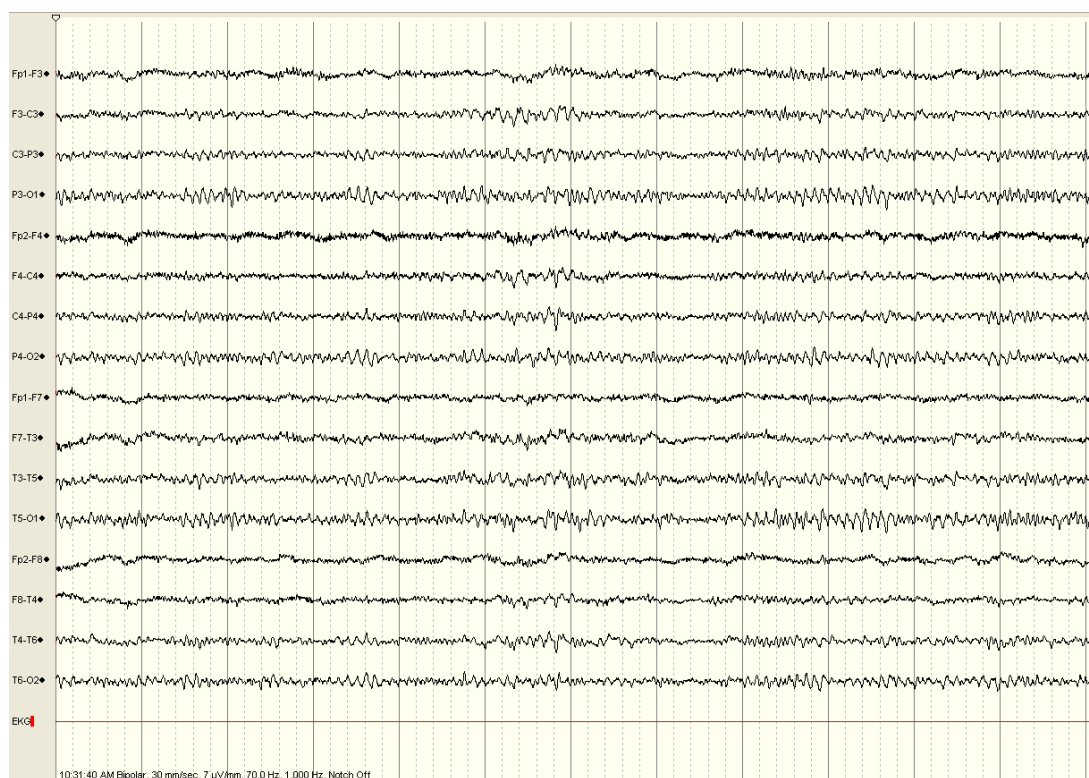
### Small Sharp Spikes

Small sharp spikes (SSS), also known as benign epileptiform transients of sleep (BETS), are common transients seen in sleep stages I and II in about 25% of adults (20). They are monophasic or biphasic and have an amplitude less than 50 µV and duration less than 50 ms. There may be an aftergoing dip in the background (slow wave), however its amplitude is less than that of the spike. SSS are unilateral, though can be reflected on the contralateral hemisphere. At times their polarity is complex, with an oblique dipole extending over both hemispheres (Figure 11.19). They are best seen in

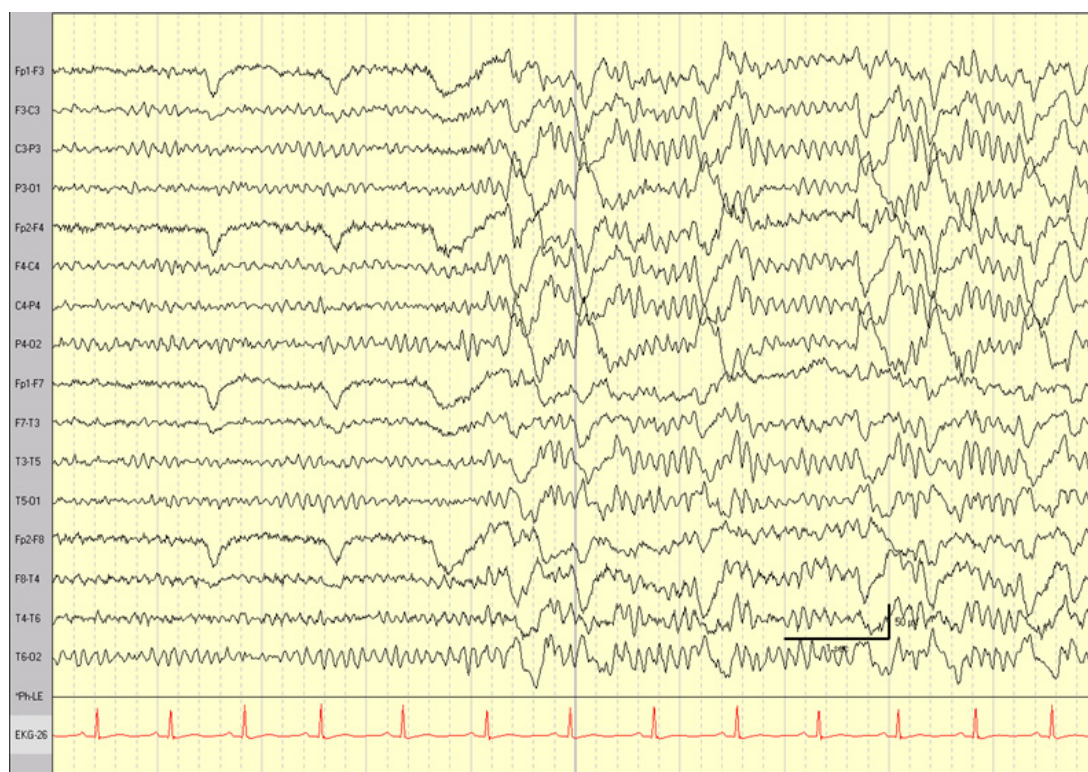




**FIGURE 11.16** Slow alpha variant is noted in the 4th to 8th second; it has a frequency of 5 Hz and has a notched appearance. In the initial part of the tracing, a 10 Hz background is noted.



**FIGURE 11.17** Fast alpha variant with a frequency of about 20 Hz is noted admixed with the more common 10 Hz background.

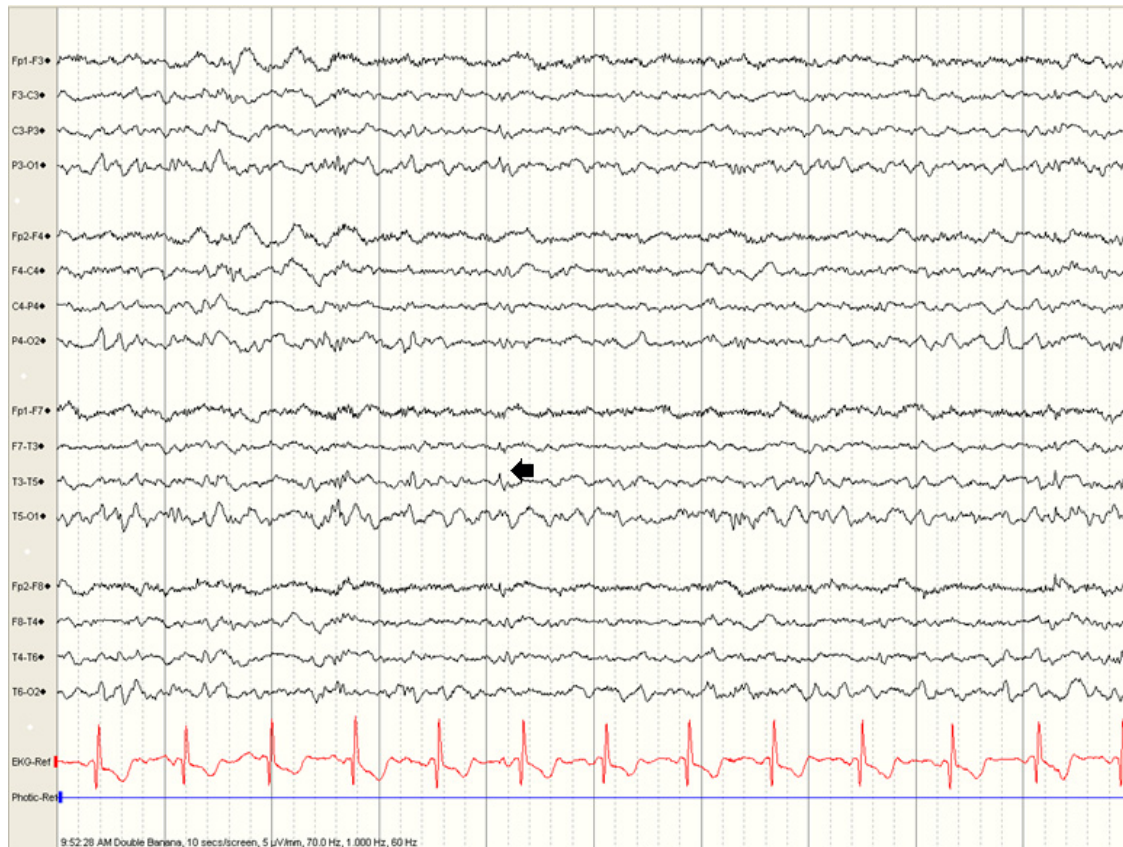


**FIGURE 11.18A** A subclinical rhythmic electrographic discharge in adults starting with a burst of delta waves that interrupt the background.



**FIGURE 11.18B** This is the page after Figure 11.18A. The rhythmic discharge continues with evolving frequencies for about 90 seconds.





**FIGURE 11.19** A small sharp spike is shown (arrow) with complex polarity.

a referential montage with long interelectrode distances. SSS do not occur in runs, nor is there associated focal slowing. It is important not to confuse SSS with epileptiform spikes as they are not associated with epileptogenicity and are considered a normal variant.

### Fourteen- and Six-Hertz Positive Bursts

Fourteen- and six-hertz positive bursts, previously called ctenoids, consist of short (0.5 to 1 second) runs of positive sharp waves that are best seen over the temporal areas but have a widespread field. The bursts have either a 14-Hz (13 to 17 Hz) or a 6-Hz (6 to 7 Hz) frequency, though the 14-Hz discharges are more common. They are best visualized in a referential montage with long interelectrode distances. Between the spiky positive components is a rounded negative phase (Figure 11.20). These discharges are seen mostly in drowsiness and light sleep and occur mostly in adolescents and young adults and decrease with age. They can be differentiated from epileptiform spikes by their distribution, lack of aftergoing slow wave, and typical morphology.

### Six-Hertz Spike and Wave Bursts

Six-hertz spike and wave bursts are runs of bilaterally synchronous bursts of spike and slow wave discharges occurring

at a frequency of 5 to 7 Hz, mostly 6 Hz. The spike is often low amplitude and buried in the slow wave, hence the previous name, phantom spike and wave. The bursts last 1 to 2 seconds and occur in relaxed wakefulness and drowsiness, disappearing in deeper stages of sleep (Figure 11.21). They are mostly seen in adolescents and young adults, becoming less common in older adults.

Two types of 6 Hz spike and wave bursts have been described (21). The FOLD (female, occipital, low amplitude, drowsy) variety is thought to be a benign variant. The WHAM (wake, high amplitude, anterior, male) variant is more likely to be associated with epilepsy. Slower discharges with a high-amplitude spike component are more likely to be abnormal and associated with epilepsy.

### Wicket Spikes

Wicket spikes are sharp waves that are usually between 90 and 150 ms in duration and less than 200 µV in amplitude. They occur in runs or in isolation independently in both temporal regions during drowsiness and light sleep. Wicket spikes can be differentiated from epileptiform spikes by the lack of aftergoing slow waves, no associated slowing, disappearance in deeper stages of sleep, and no disruption of underlying background (Figure 11.22). Isolated wicket spikes can be correctly recognized by comparing their morphology



FIGURE 11.20 Burst of 14-Hz positive spikes (arrow) displayed in a contralateral ear referential montage.

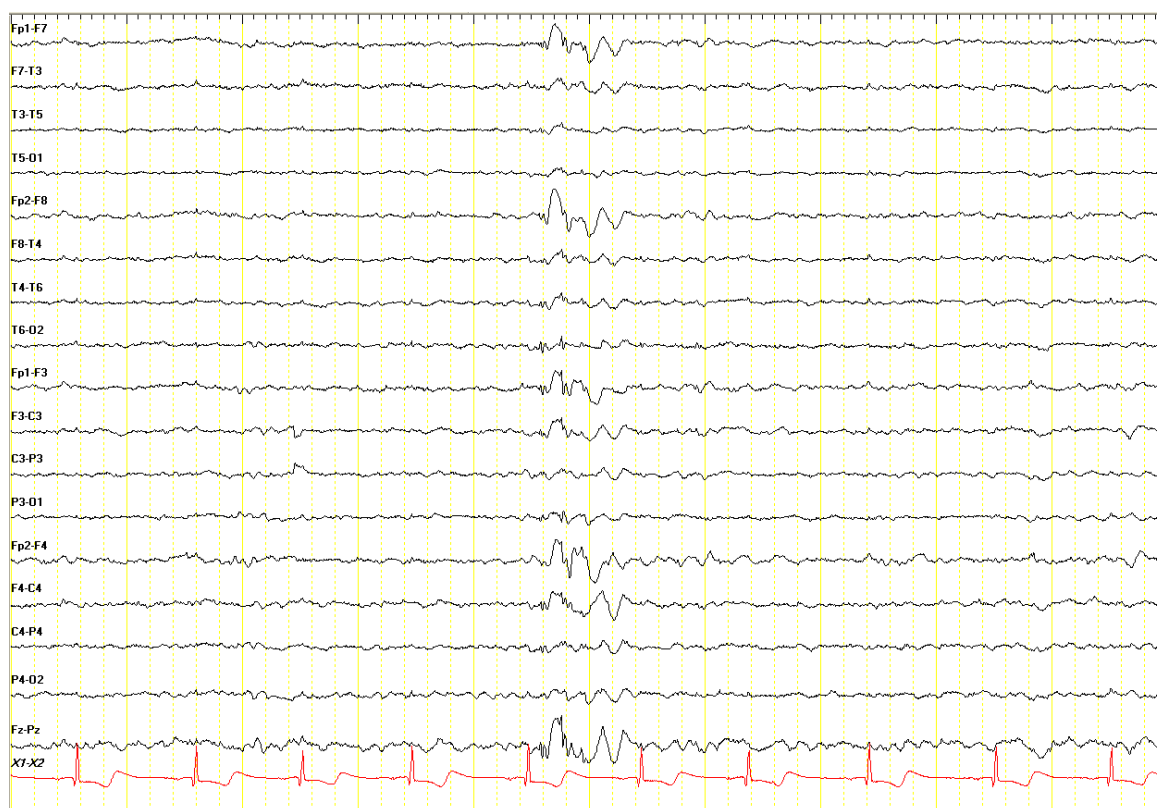
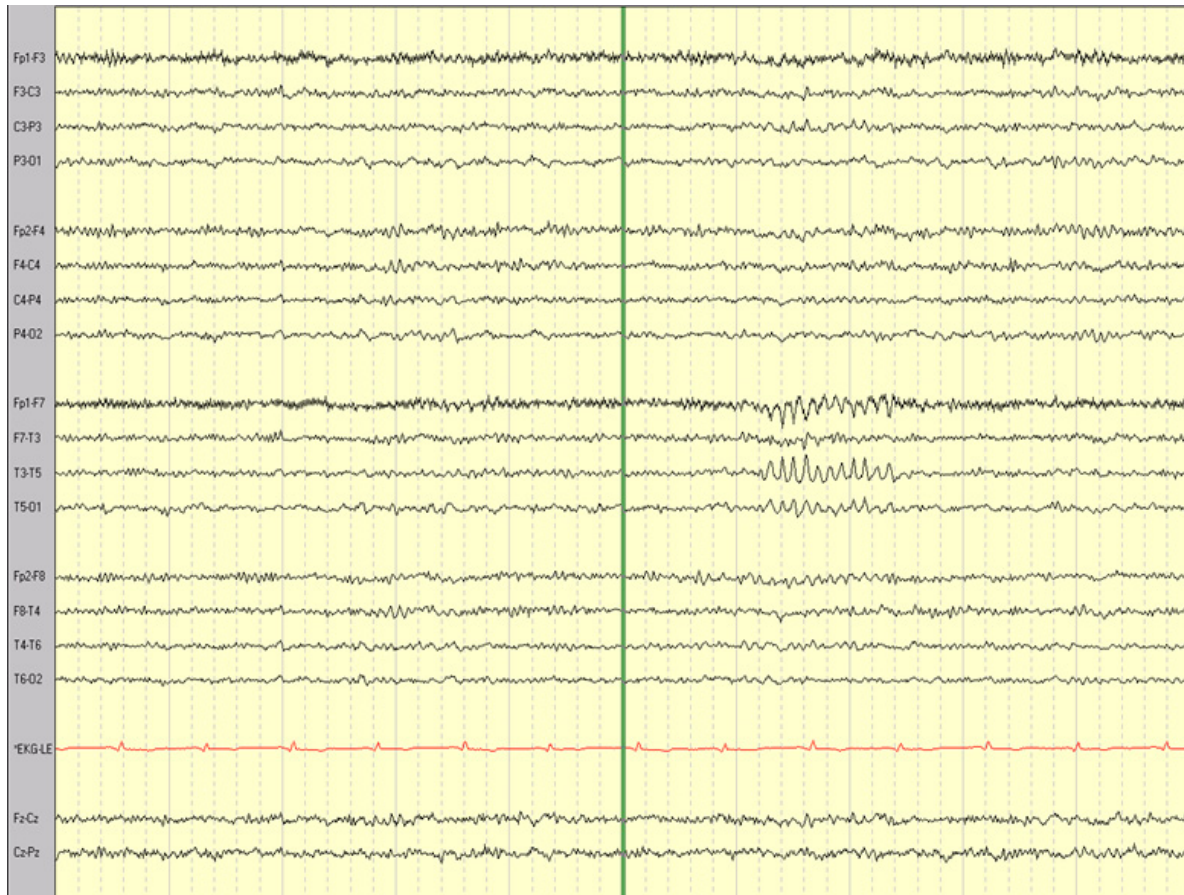


FIGURE 11.21 Burst of 6-Hz spike and wave discharge seen best frontally.



**FIGURE 11.22** Burst of wicket spikes in the left temporal region.

to that of a train of wicket spikes, which will be similar. It is widely thought that wicket spikes are fragmented temporal alpha rhythm and a normal variant (10).

### Breach Rhythm

Breach rhythm is seen over areas of a skull defect. Since bone acts as a high-frequency filter, EEG overlying a skull defect has higher amplitude and faster frequencies compared to the other side (Figure 11.23). Highest amplitude breach rhythm is seen over the central region, where the amplitude may be three times as high as the other side. This may make underlying mu rhythm and wicket spikes look deceptively abnormal. Similarly, single sharply contoured waveforms may look epileptiform. The absence of an aftergoing slow wave, lack of spread to adjacent areas, and disappearance of this activity in deeper stages of sleep should alert one to their benign nature. Breach rhythm is not abnormal and does not signify epilepsy or other pathology. It should be noted, however, that breach rhythm is often associated with focal slowing from underlying brain injury. In such a case, the focal slowing is considered abnormal but the breach rhythm is not.

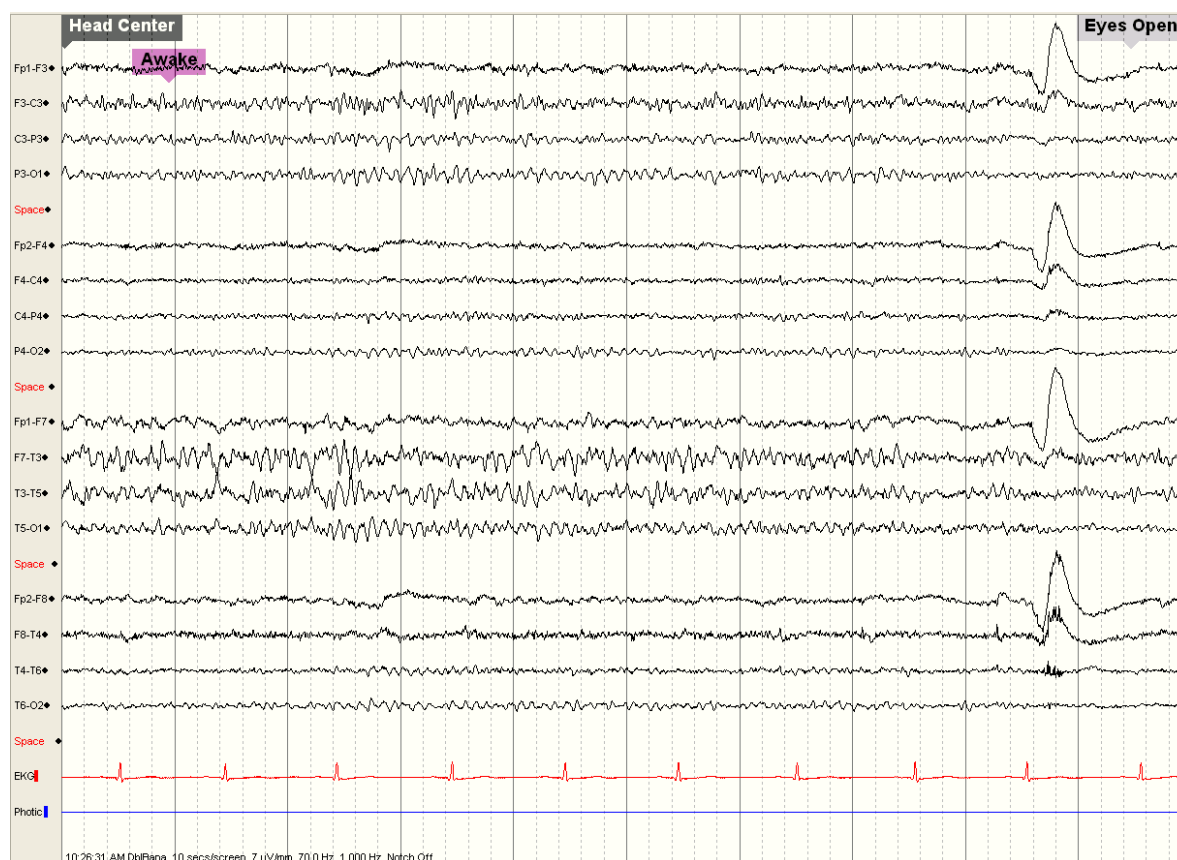
## ARTIFACTS

There are many types of artifacts that can occur in an EEG, and the most common ones will be discussed here. Artifacts can be divided into biological (arising from within the patient, but not the brain) and nonbiologic (arising from the environment). Attention to technical detail can minimize the occurrence of artifacts, but, sometimes, despite careful preparation, they are still seen. One of the foremost responsibilities of the electroencephalographer is to recognize these artifacts and not misinterpret them as abnormalities. To this end, understanding that abnormalities have a typical topographic field and particular characteristics is of critical importance. In addition, the technologist's notations can be extremely helpful in identifying artifacts.

### Electrocardiographic Artifact

The electrocardiogram (ECG) is usually recorded in a dedicated channel in most EEG. However, it often appears in EEG channels as a biologic artifact. When the ECG is recorded in a separate channel, the artifact is easy to identify by noting its occurrence with the ECG. The ECG artifact is seen most





**FIGURE 11.23** Breach rhythm seen over the left centrotemporal region manifest as higher voltage, sharper activity compared to other side.

often in montages with long interelectrode distances, such as referential montages, particularly when A1 or A2 are used as the reference. One ear represents the negative end (usually A2) of the cardiac dipole and the other ear the positive end (usually A1) (5). Obese patients, those with short necks, and neonates are more likely to have prominent ECG artifacts. This artifact can be reduced by linking A1 and A2, by using Cz as a reference, or by changing the position of the head (ie, extension).

### Pulse Artifact

Pulse artifact is a biologic artifact consisting of a slow wave that is time-locked to ECG, occurring about 200 ms after the QRS peak. It occurs when an electrode is placed over an artery, especially when the electrode is applied loosely. Pulse artifact is usually confined to one electrode. Though it can be confused with focal slowing, pulse artifact can be recognized by its association with the ECG rhythm.

### Eye Movement Artifact

Eye movement artifact occurs because the cornea is positively charged compared to the retina. Thus, whenever the cornea

moves closer to one electrode, a positive deflection occurs in that electrode. When the eyes move upward, a downward deflection is noted in the frontal leads; when the eyes move laterally, out-of-phase deflections are noted in F7/F8 electrodes. As noted previously, eye movement artifact can be helpful in identifying REM sleep and wakefulness.

Asymmetry of eye movement artifact can occur due to several reasons. Placement of frontal leads that are not symmetric is a common cause of such asymmetry. Enucleation of one eye will result in absence of artifact noted on that side (Figure 11.24). A skull defect over one frontal region will cause the eye movement artifact on that side to have higher amplitude (22).

When persistent frontal delta activity is seen, such as frontal intermittent rhythmic delta activity (FIRDA), additional leads should be placed below the eyes (eye leads). These leads will help differentiate frontal delta activity from eye movements (such as flutter). Eye movement activity will be out of phase in the eye and frontal leads referenced to ipsilateral ear; when the eyes move upward, a positive deflection is seen in the frontal leads and a negative deflection in the eye leads. On the other hand, FIRDA will be in phase in both leads as both leads will have the same polarity. Whereas most activity that is out of phase in the eye and





**FIGURE 11.24** Unilateral eye blinks in a patient with enucleation of right eye.

frontal leads arises from the eyes, an exception is frontopolar spikes or slow waves. These will have opposite polarity in the eye and frontal leads, leading to out-of-phase activity.

### Electromyographic Artifact

Electromyographic (EMG) artifact is another common biologic artifact. It often occurs as repetitive single motor units that have either a positive or negative deflection; this is referred to as a comb-like appearance. This type of EMG artifact is usually confined to one electrode as nearby electrodes will not display the same motor unit. It is a low-amplitude potential that has a duration typically less than 50 ms (Figure 11.25). If the high-frequency filter is reduced, it can make the EMG artifact look like epileptiform spikes; this is discouraged. EMG artifact is commonly seen in the temporal leads (from the underlying temporalis muscle). Asking the patient to relax her/his jaw often eliminates it. Another common location of this artifact is the frontal leads (from the underlying frontalis muscle). Photoc stimulation can produce contraction of the frontalis muscle that will be recorded from the frontal leads. This produces the photomyoclonic response described previously. Persistent contraction of underlying muscles can produce excessive

EMG artifact that can make the underlying EEG unable to be interpreted.

### Lateral Rectus Spikes

Lateral rectus spikes are a type of EMG artifact that occur with contraction of the lateral rectus muscle. The spikes are low-amplitude, short-duration discharges that have a rapid upslope and a slower downslope. They are best seen in frontal electrodes and often occur with eye movements (Figure 11.26). They must be differentiated from frontal spikes; lateral rectus spikes do not have an aftergoing slow wave, are often seen with eye movements, are limited to frontal electrodes, and disappear in sleep.

### Glossokinetic Artifact

Glossokinetic artifact occurs when there is tongue movement. The tip of the tongue is negatively charged compared to its base. Thus, when the tongue moves, artifact can be seen on scalp electrodes. The artifact is best seen along the temporal chain; however, it can vary depending on the position of the tongue. It consists of a burst of delta activity accompanied by EMG artifact. (Figure 11.27)

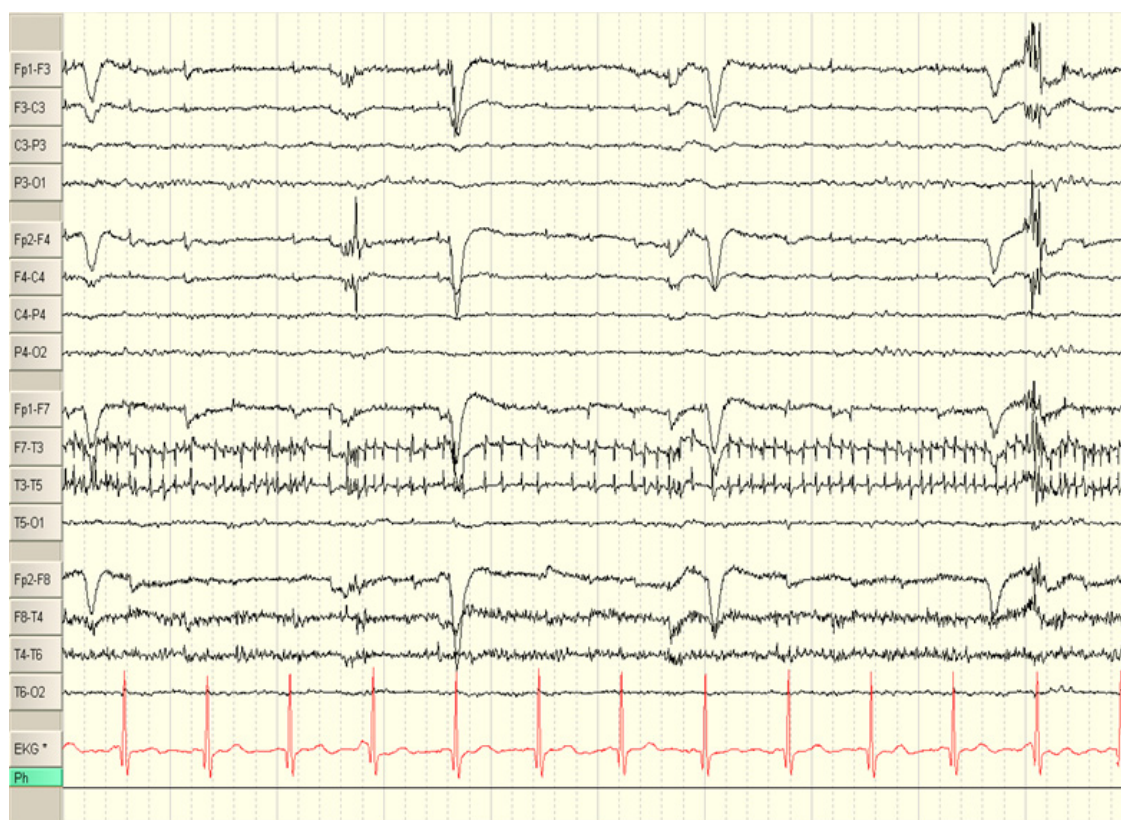
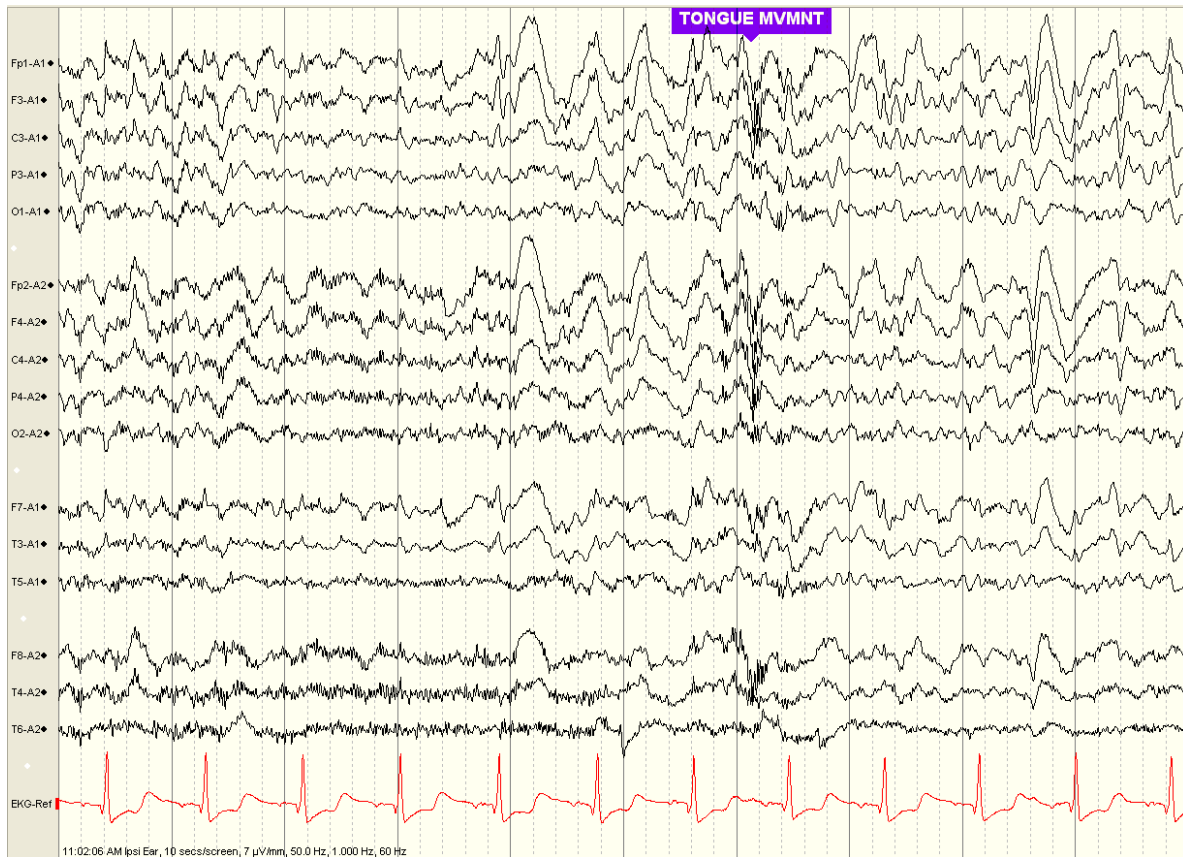


FIGURE 11.25 Comb-like EMG artifact arising from T3 electrode.



FIGURE 11.26 Lateral rectus spikes seen in frontal leads (arrow).





**FIGURE 11.27** Glossokinetic artifact noted with swallowing.

### Sweat Artifact

Sweating produces a very slow discharge (less than 1 Hz) that can often be reduced with low-frequency filters. This type of artifact can be seen in patients who are febrile or sweating excessively for any other reason. Cooling the room may help in reducing sweat artifact. At times, excessive sweating can produce salt bridges between adjacent electrodes producing a false voltage asymmetry.

### Electrode Artifact

Electrode artifact, also known as electrode pop, is a type of nonbiologic artifact that produces discharges that look remarkably different from cerebral potentials. They are typically confined to the single electrode that is at fault. At times, it can produce a high-amplitude negative phase reversal between two channels in a bipolar montage, resembling a spike (Figure 11.28). It should be differentiated from a spike by its very restricted field (confined to a single electrode), its association with other bizarre-looking discharges in the same channels, and disappearance with reapplication of the electrode. These artifacts most commonly result from poorly applied electrodes but can also occur due to a broken electrode wire, drying of electrode gel, or change in the scalp–lead interface (22). When an electrode artifact is seen,

the technologist should reapply the electrode, and if it does not disappear, replace it.

### Environmental Artifact

Environmental artifacts are another type of nonbiologic artifact that can be very challenging to isolate. They are often seen in hostile recording environments such as intensive care units or the operating room. Common examples include 60-Hz line artifact, drip artifact from intravenous bags, respirator artifact, and rhythmic artifacts generated by percussion beds. The technologist is instrumental in helping correctly identify these artifacts (ie, by noting the cycles of the respirator or percussion bed, by applying additional electrodes to an intravenous solution line to directly record that artifact, and displaying it in a separate channel).

A normal EEG is often considered the easiest type of EEG to interpret. The simplicity can be deceptive, however. The wide range of normal, rhythmic, and sharply contoured normal variants, and artifacts that resemble cerebral activity make interpretation of these studies much more challenging. When normal patterns are interpreted as epileptiform, patients are inappropriately subjected to years of antiepileptic drug therapy. Familiarity with these



**FIGURE 11.28** Electrode artifact in T5 electrode manifesting as negative (short arrow) and positive (long arrow) phase reversals.

variations of normal is critical for anyone who interprets EEG data. It should be remembered that it is not the absence of normal features but the presence of abnormal ones that makes an EEG abnormal.

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# EEG of Epilepsy

*Rajdeep Singh*

EEG is largely a recording of excitatory and inhibitory postsynaptic potentials generated by the large vertically oriented pyramidal neurons located in layers 3, 5, and 6 of the cerebral cortex. The EEG recording has limited specificity in terms of localization and spatial analysis as various factors such as dipole orientation, volume conduction, synchronization, and evolution of ictal activity can influence the final recording. However, despite advances in medical technology, including functional neuroimaging and recording magnetic brain field with magnetoencephalography (MEG), EEG remains the mainstay for the diagnoses and monitoring of epileptic activity. In this chapter, interictal and ictal EEG patterns for common types of epilepsies will be discussed.

## EPILEPTIC ACTIVITY—GENERAL CONSIDERATIONS

### Interictal Epileptiform Activity

Interictal epileptiform discharges (IED) can present as single spikes, sharp waves, or complexes that contain spikes and sharp waves that can last for up to a few seconds. In addition, IEDs can also present as intermittent rhythmic focal slowing such as temporal intermittent rhythmic delta activity (TIRDA) in adults or occipital intermittent rhythmic delta activity (OIRDA) in children.

Epileptic spikes are sharply contoured waveforms with lasting between 20 and 70 ms (Figure 12.1). Sharp waves, by contrast, are not as sharply contoured and last for 70 to 200 ms. The clinical importance of distinguishing between spikes and sharp waves is uncertain. Epileptic spikes and sharp waves are commonly surface negative due to the depolarization of the superficial laminae (1). They are episodic and should clearly stand out from the underlying background activity. Often they disrupt the underlying background activity and can have an aftergoing slow wave, to form a spike-and-wave complex. Spikes and sharp waves should also have a voltage field, which should make biological sense

in regard to the underlying location of the cortical source. Analyzing the voltage field can help distinguish them from artifacts. It is also important to distinguish epileptiform activity from normal variants such as vertex waves, lambda waves, and wicket spikes.

### Ictal Activity

Electrographic seizures or ictal patterns can be a longer-lasting epileptiform activity or an electrographic deviation from the baseline that shows an organized, rhythmic pattern and has evolved in terms of frequency, field or distribution, morphology, and amplitude.

EEG findings can be very useful in distinguishing between different epilepsies and remains integral part of syndromic classification. Ictal recordings can provide further data in characterizing and quantifying seizure types over the interictal findings. The ictal recording is also indispensable when considering surgical treatment for epilepsy.

## EEG OF LOCALIZATION-RELATED EPILEPSIES

Localization-related epilepsies have several types of abnormal EEG findings, including focal IEDs and slowing. The type of seizure depends on the seizure-onset zone, though the clinical manifestations can be from the spread of ictal activity. It is important to recognize that occasionally the EEG can be normal in a focal seizure. The cortical region of synchronous activity needs to be at least 6 cm<sup>2</sup> (1) and create changes on the surface of the cortex large enough to be picked up by scalp electrodes.

### Benign Epilepsy With Centrotemporal Spikes

Benign epilepsy with centrotemporal spikes (BECTS), previously also referred to as benign rolandic epilepsy (BRE), has characteristic interictal EEG abnormalities. The background EEG is normal. Typical central-midtemporal spikes



**FIGURE 12.1** Interictal spikes as may be seen in localization-related epilepsy.

are seen with maximal voltage in the C3/4 electrodes and a field that extends to the T3/4 electrodes when viewed in a longitudinal bipolar montage. The spikes are stereotyped, diphasic (occasionally triphasic), and often have a horizontal anterior-posterior dipole with frontal positivity rather than a typical vertical dipole that is brain surface negative (Figure 12.2). They can occur singly or in runs, especially accentuated in light non-REM sleep. It can be easier to differentiate them from vertex waves by looking at them in transverse bipolar montage.

### Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common form of localization-related epilepsies. Mesial temporal lobe onset accounts for majority of the temporal lobe seizures. Interictal EEG findings in mesial temporal lobe epilepsy (MTLE) show anterior temporal lobe discharges along with intermittent temporal slowing (Figure 12.3). Voltage of the IEDs is maximal in the sphenoidal or “true” anterior temporal electrodes (T1, T2) (2). Epileptiform discharges with maximum voltage in the lateral temporal leads can be seen, however, their predominance should raise the suspicion for a neocortical or extra mesial temporal generator (3). In approximately

one-third of the patients, IEDs can be bilateral (2,4). TIRDA is seen only in minority of the patients, but when present, is highly associated with temporal lobe epilepsy (3).

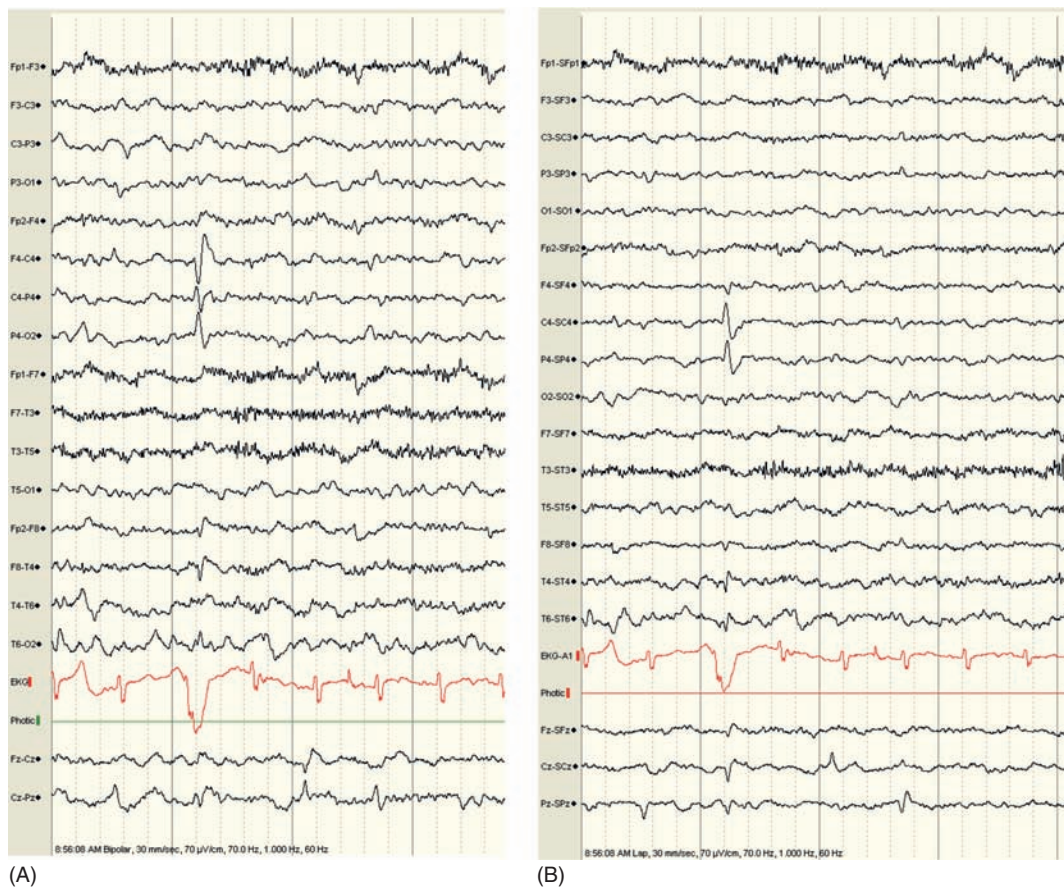
The characteristic ictal EEG pattern of MTLE consists of unilateral 5- to 9-Hz rhythmic ictal theta or alpha epileptiform activity maximal in the anterior temporal scalp electrodes (3) (Figure 12.4). This pattern appears about 30 seconds after onset of clinical symptoms and signs (2). Post-ictal focal slowing or attenuation on the side of the seizure onset is more commonly seen in MTLE than with partial seizures originating outside the temporal lobe (2).

The EEG features of neocortical temporal lobe epilepsy tend to be more broadly distributed and less specific than those of MTLE. The IEDs are more likely to be lateral temporal, but these can be difficult to differentiate from MTLE IEDs (5). The ictal pattern is widely distributed in the hemisphere at onset and consists of an irregular, polymorphic rhythmic delta activity. Spread to contralateral hemisphere tends to develop earlier and more often than the MTLE (6) (Figures 12.5A and 12.5B).

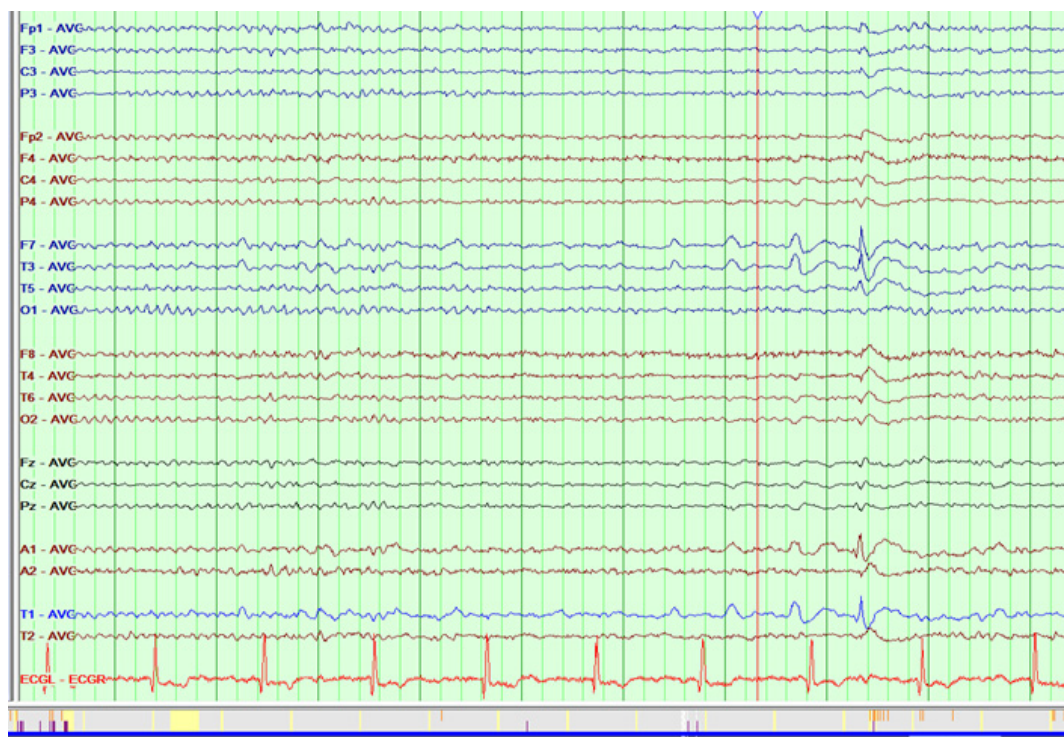
### Frontal Lobe Epilepsy

Frontal lobe epilepsies frequently lack lateralizing or localizing features on scalp EEG. Often, especially with mesial



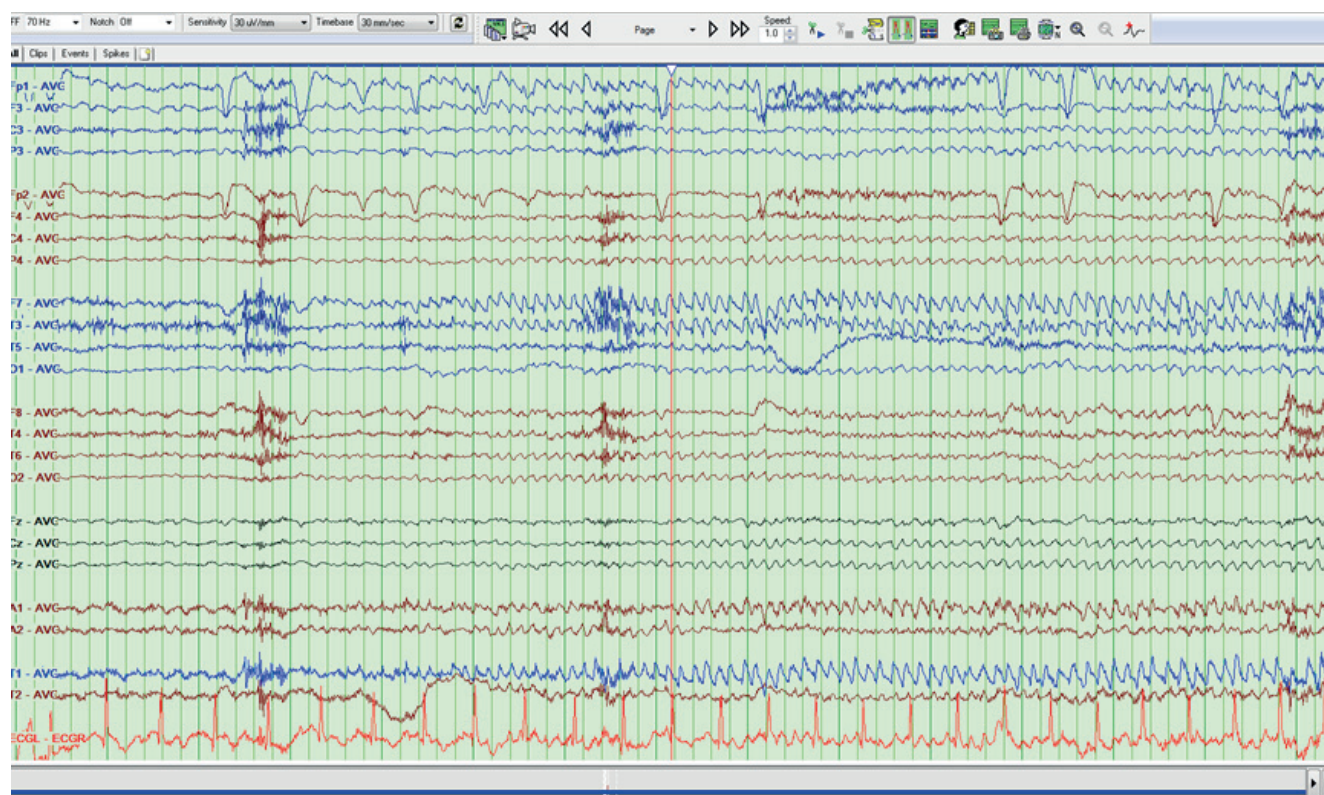


**FIGURE 12.2** A central spike of benign epilepsy with centro temporal spikes (BECTS), (A) shows the spike in a longitudinal bipolar montage and (B) shows it in a Laplacian montage. Note the horizontal dipole with frontal positivity.

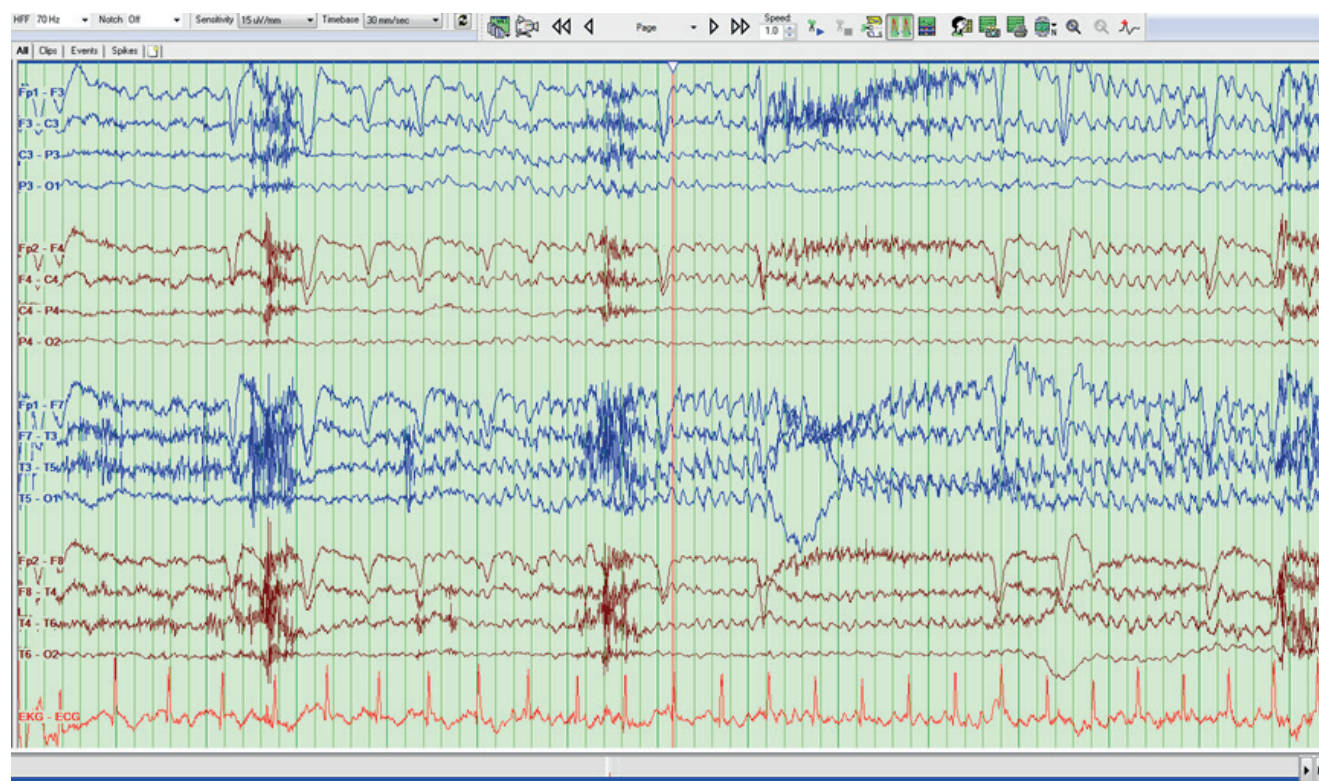


**FIGURE 12.3** Left anterior temporal sharp waves and spike in an average reference montage.





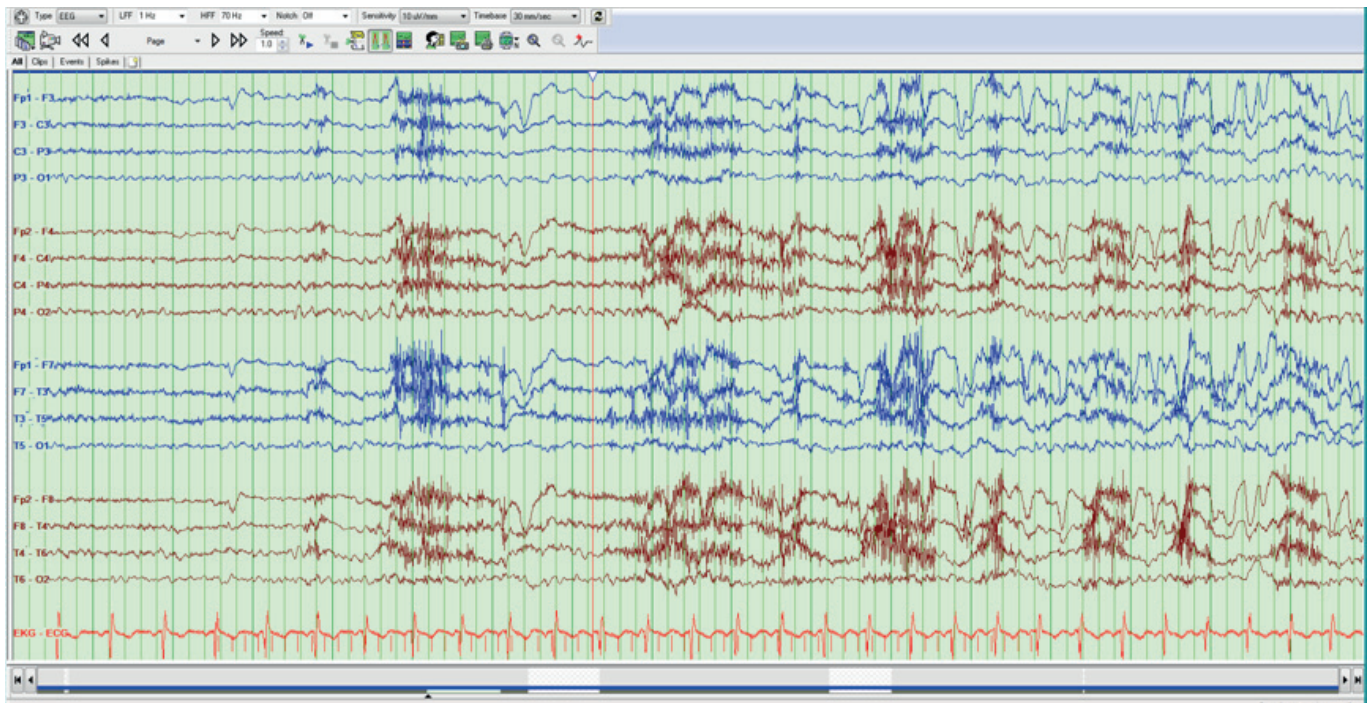
(A)



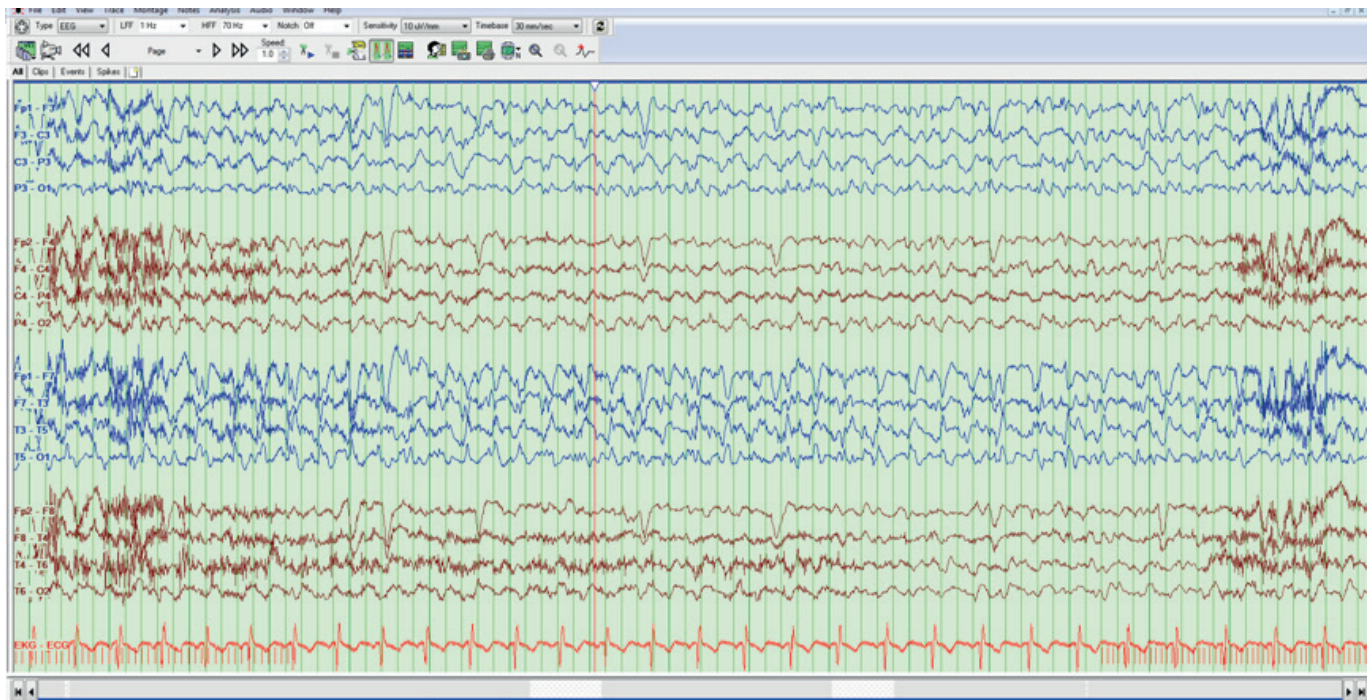
(B)

**FIGURE 12.4** Rhythmic ictal theta in the left anterior temporal leads representing the onset of a temporal lobe seizure. (A) Demonstrates this in an average referential montage. (B) Shows the same seizure in a longitudinal bipolar montage.





(A)



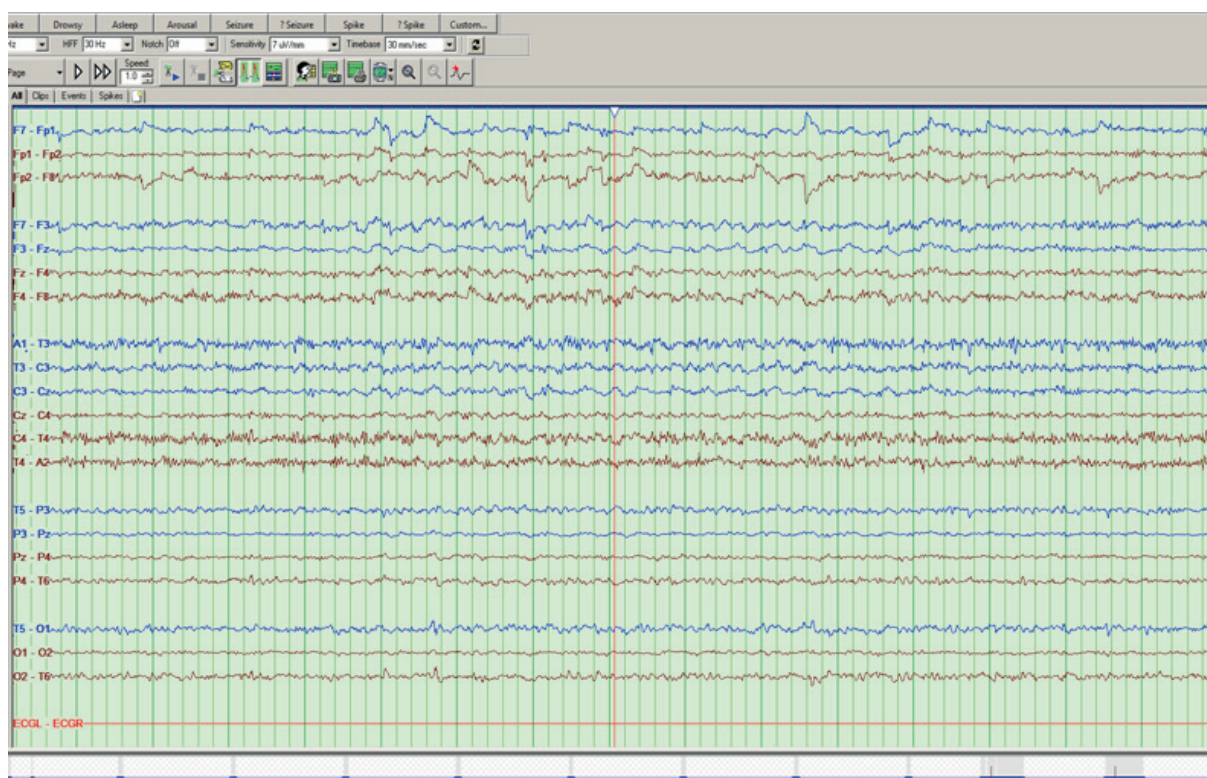
(B)

**FIGURE 12.5** Left neocortical temporal seizure shown in a longitudinal bipolar montage. Notice the slower rhythmic activity over the temporal leads. The patient had lateral temporal focal cortical dysplasia.

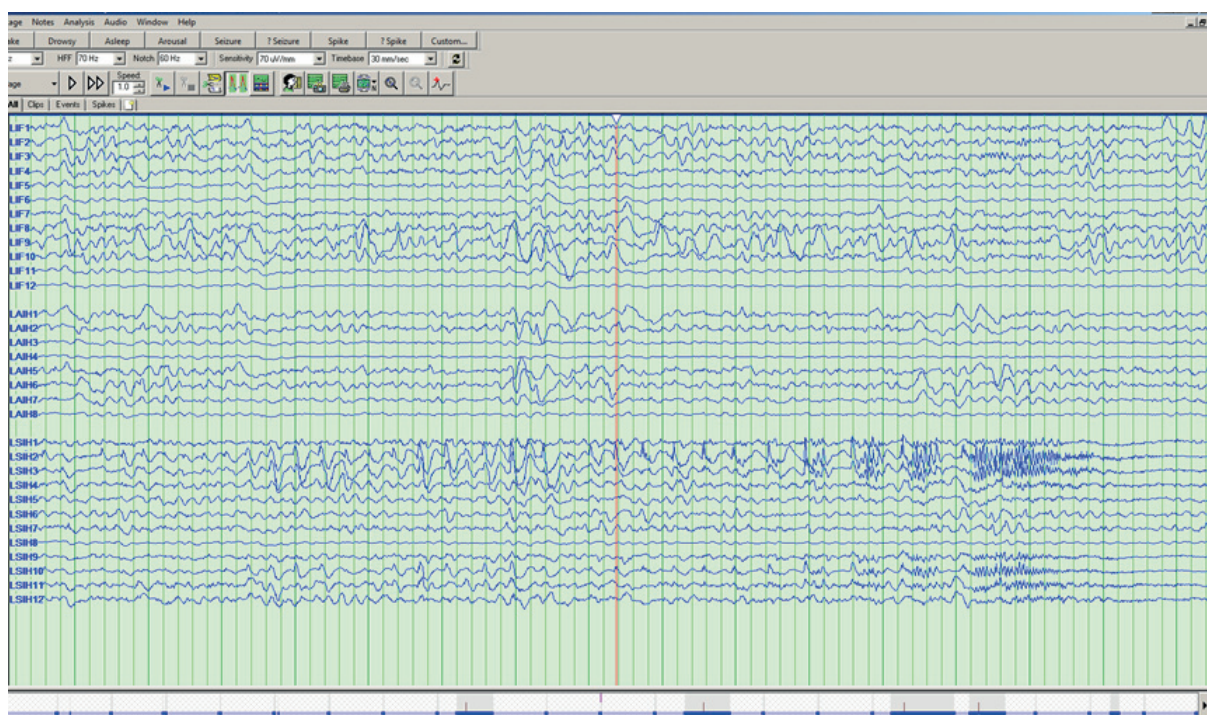
frontal lobe epilepsies, there is no electrographic correlate on the scalp electrodes (Figure 12.6). The IEDs, when present, can be bilateral synchronous, multifocal, or lateralized to the temporal lobe (7). Patients with mesial frontal lobe

epilepsy can have rhythmic midline theta during wakefulness or bilateral frontal synchronous discharges (8). It is important to exclude periods of drowsiness and mental activation when evaluating rhythmic theta activity. Midline or





(A)



(B)

**FIGURE 12.6** This is a mesial frontal lobe seizure. (A) Shows scalp EEG in a transverse bipolar montage that has no clear electrographic correlate except for possible subtle slowing in the left fronto-central leads. (B) Shows the same seizure with subdural electrodes showing spikes and seizure onset in the left inter-hemispheric subdural strip electrode (LSIH).



frontocentral IEDs can be seen from electrodes Fz, Cz, F3, and F4 (9), but again need to be differentiated from sleep and drowsiness. IEDs from dorsolateral frontal cortex are more likely to be present and lateralized.

Ictal onset for frontal lobe seizures is challenging due to the presence of prominent muscle artifact seen with the hypermotor activity. Occasionally, seizure patterns may be evident at the midline electrodes where EMG activity is minimal. Rhythmic epileptiform delta activity can be seen at the onset from dorsolateral frontal lobe seizures. About 25% of frontal lobe epilepsy surgical patients have focal beta frequency discharge at onset on scalp EEG. The presence of this focal beta activity is highly correlated with postsurgical seizure control (10).

### Parietal Lobe Epilepsy

Parietal lobe epilepsy is much less common than temporal or frontal lobe epilepsy. The conventional scalp EEG is of limited utility in these cases as the discharges are rarely localized. Interictal discharges can project to frontal or occipital head regions, causing false localization. Secondary bilateral synchrony of interictal discharges has been reported in more than 30% of patients undergoing surgery (11). Seizures are also rarely localized, though can be lateralized.

### Occipital Lobe Epilepsy

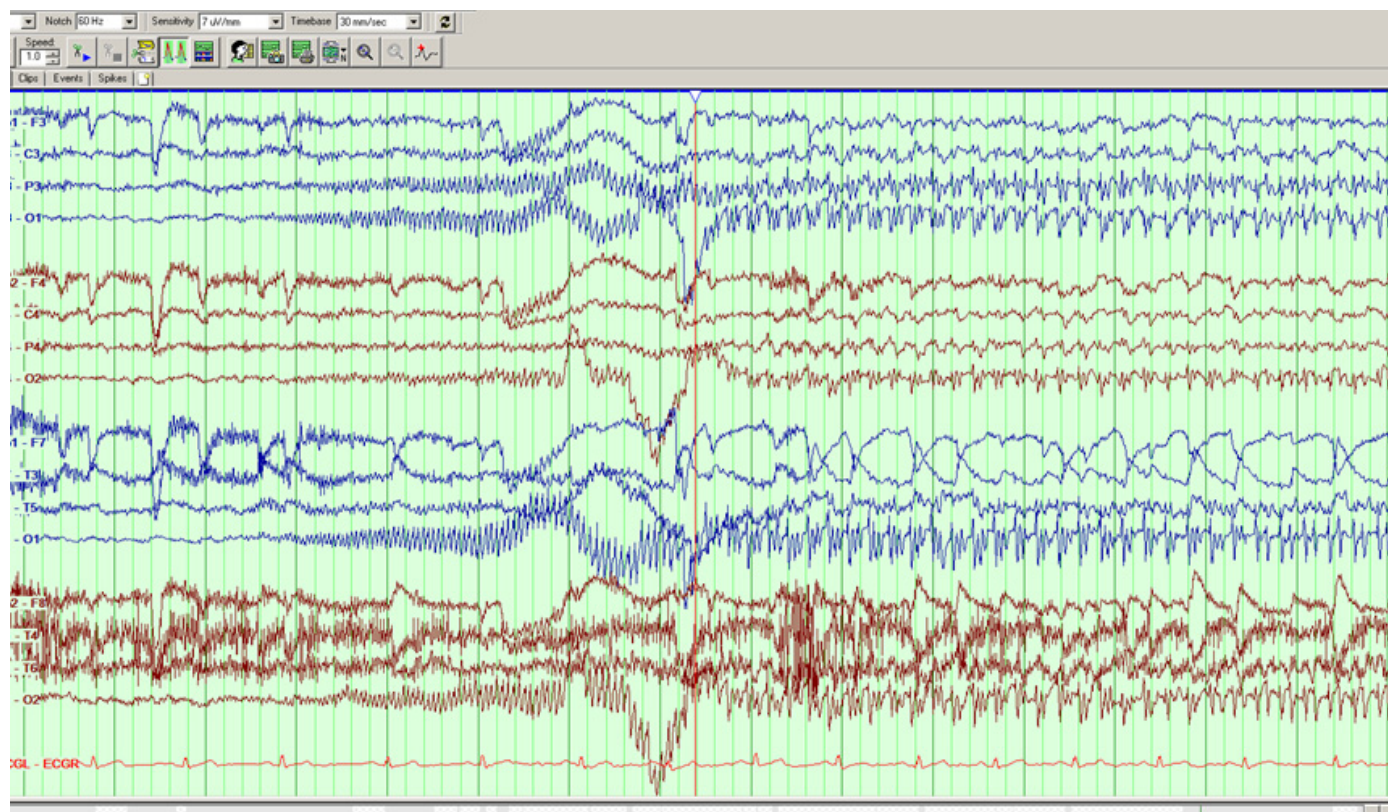
Interictally, spontaneous or photic-induced occipital spikes are the main abnormalities in idiopathic occipital lobe epilepsy. However, it is important to keep in mind that occipital spikes can occur normally in 0.9% of preschool age children (12). Ipsilateral occipital slowing is more common than spikes in cryptogenic or symptomatic occipital lobe epilepsy. This can present as asymmetrical physiological rhythms such as alpha, lambda waves, photic driving, or positive occipital sharp transients of sleep.

Ictal manifestation is in the form of paroxysmal fast activity, fast spiking, or both, localized to the occipital regions with occasional gradual anterior spreading and generalization with spike-wave discharges (Figure 12.7).

### EEG OF GENERALIZED EPILEPSIES

#### Childhood and Juvenile Absence Epilepsy

The classic EEG finding in childhood absence epilepsy is a generalized high-amplitude surface negative 3 Hz (range 2.5 to 5 Hz) spike and slow wave discharges (Figure 12.8). The discharges are most prominent in the frontal or frontocentral regions. Prominent OIRDA may also be present in children between the ages of 6 to 10 years (13). OIRDA is distinguished



**FIGURE 12.7** An occipital lobe seizure in a longitudinal bipolar montage.



**FIGURE 12.8** Interictal activity in patient with absence seizures showing the classic generalized 3 Hz spike wave discharge. The EEG is shown in a longitudinal bipolar montage.

from normal slow waves of youth by its persistence, disruption of the alpha rhythm, and high voltage (Figure 12.9). Hyperventilation elicits discharges in 95% of patients. Photoparoxysmal response may also occur but is not as common. During sleep, spike wave complexes may appear polyphasic embedded within the normal sleep architecture.

Ictal discharges are similar to the interictal discharges, but prolonged, unless they cause generalized tonic-clonic seizure. The discharges are fastest in the first few seconds with a gradual slowdown as the activity terminates, followed by rapid return to normal background rhythm (Figure 12.10).

Juvenile absence epilepsy has similar interictal and ictal EEG findings as noted previously except polyspike wave discharges (PSW) are more commonly seen (13). OIRD activity is not usually seen in juvenile absence epilepsy.

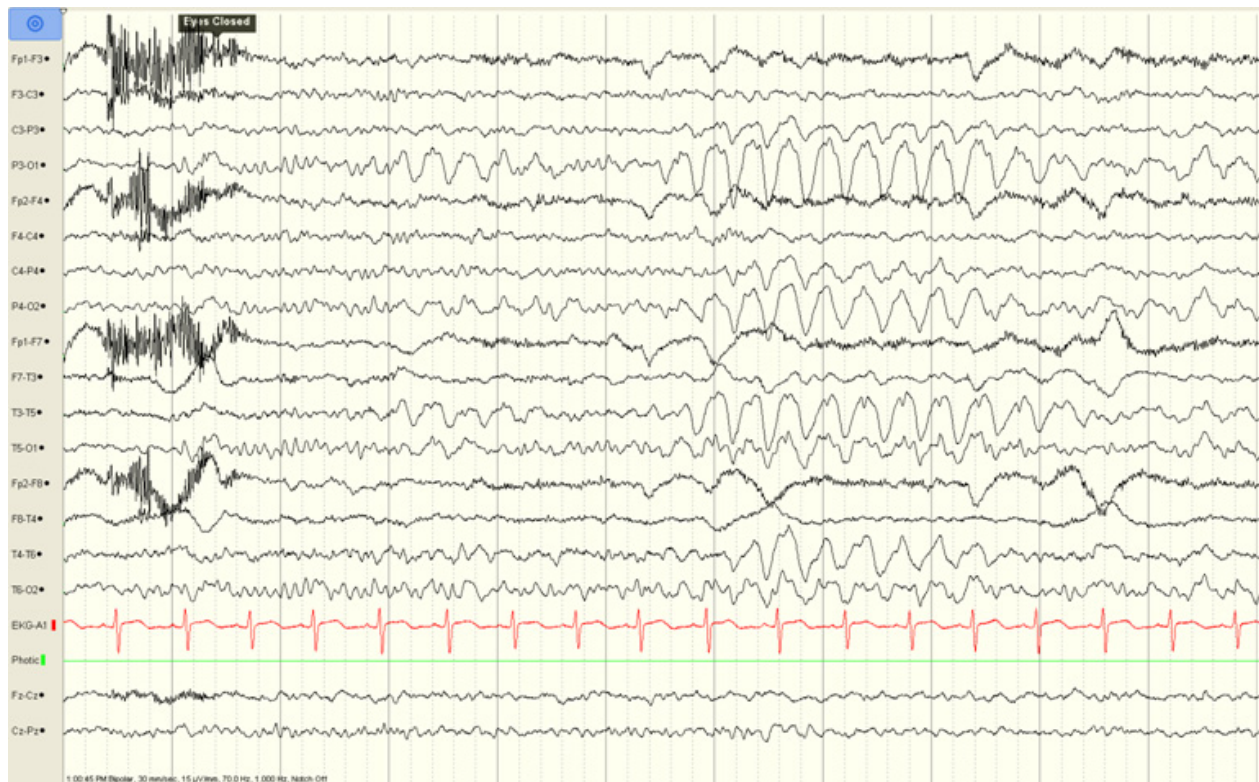
### Juvenile Myoclonic Epilepsy and Epilepsy With Generalized Tonic-Clonic Seizures Alone

EEG is highly sensitive for interictal discharges in patients with untreated juvenile myoclonic epilepsy (JME). It typically

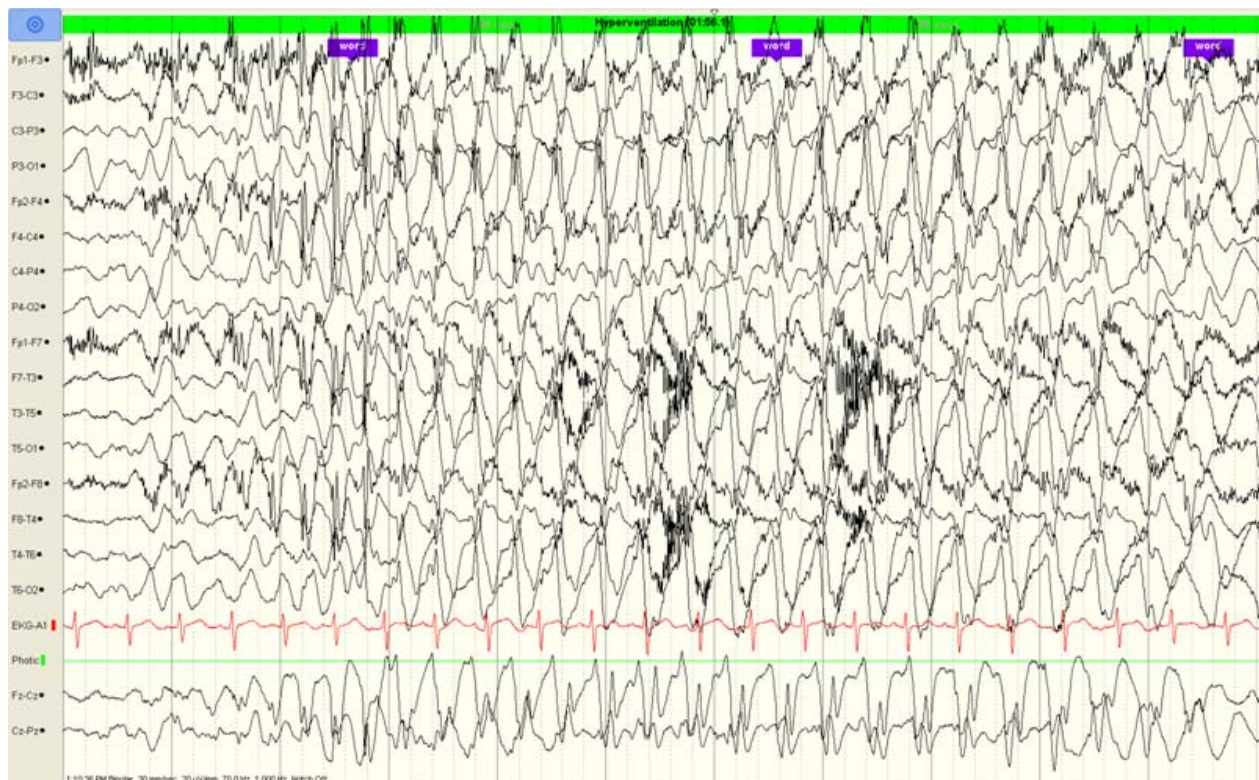
reveals a normal background with paroxysmal, generalized, bilaterally symmetric 4- to 6-Hz PSW discharges. The discharges like the generalized spike wave discharges of absence epilepsy are more prominent in the frontocentral region. Polyspikes may occur independently or in prolonged runs lasting up to a few seconds that can be followed by 2 to 5 Hz irregular high-amplitude slow waves with intermixed spikes. Photic stimulation can stimulate discharges in up to 40% of the patients (14). About half the patients have been shown to have focal or asymmetric generalized IEDs on prolonged recordings (15).

Ictally, myoclonic seizures are associated with polyspike or PSW bursts similar to the interictal discharges described earlier. Occasionally, the frequency of the multiple spikes seen is higher, about 10 to 16 Hz, with the discharges accompanied by a clinical jerk (2) (Figure 12.11). Generalized tonic-clonic seizures may be preceded by repetitive myoclonic jerks, resulting in a pattern known as clonic-tonic-clonic. The EEG during these seizures reveals 10- to 16-Hz spikes (corresponding with the myoclonus) followed by diffuse rhythmic fast activity (corresponding with the tonic phase),



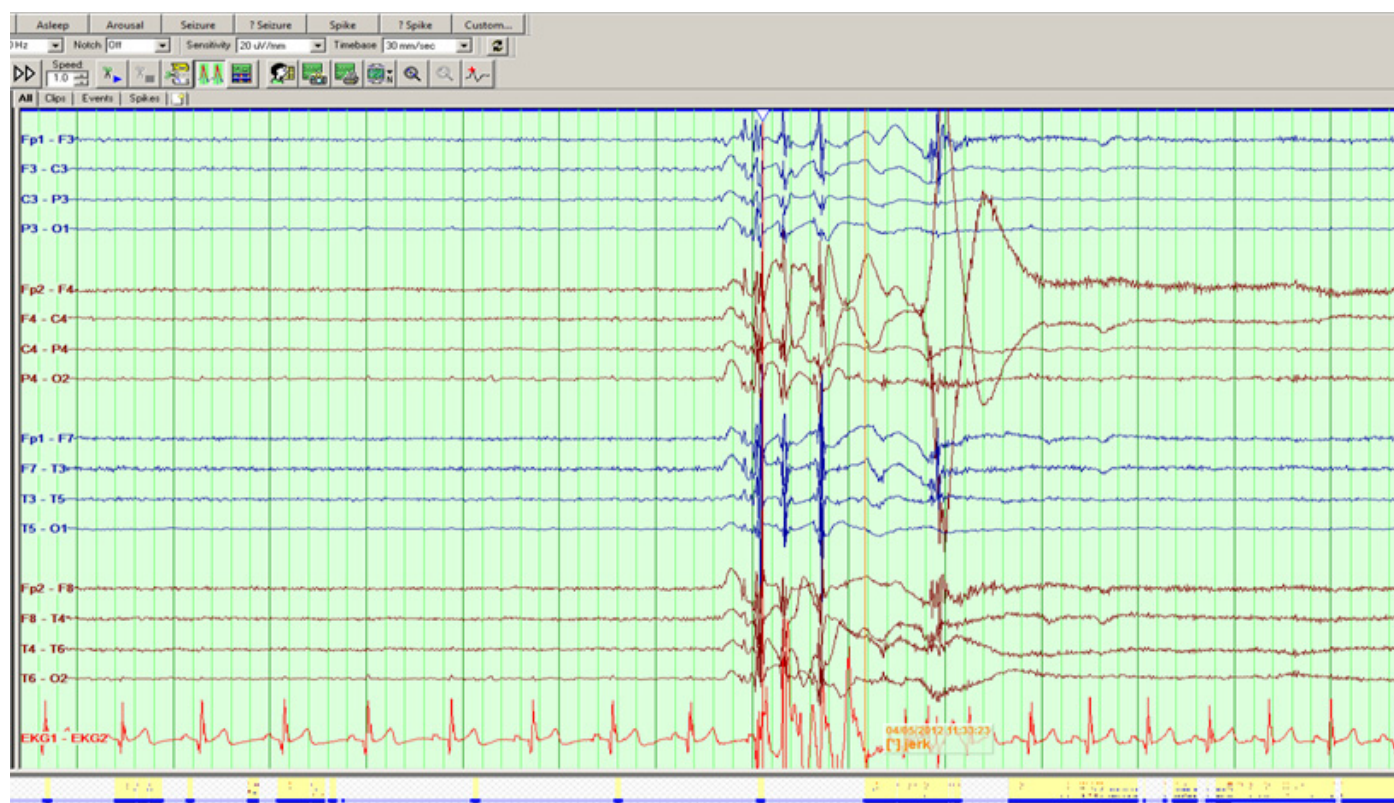


**FIGURE 12.9** This EEG in a 6-year-old girl with frequent staring spells showing occipital intermittent rhythmic delta activity (OIRDA). The EEG is shown in a longitudinal bipolar montage.



**FIGURE 12.10** This is an EEG in the same patient as Figure 12.9. The patient stops hyperventilation and stares; the EEG shows a long run of a generalized 3 Hz spike wave discharge. The EEG is shown in a longitudinal bipolar montage.





**FIGURE 12.11** EEG of a myoclonic jerk in a patient with JME. The EEG is shown in a longitudinal bipolar montage.

followed by rhythmic slow wave discharges (corresponding with the clonic phase) (Figure 12.12).

### Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is a severe epilepsy syndrome in which there are several types of seizures and cognitive impairment. The interictal EEG shows slowing of the background rhythms. IEDs are typically generalized “slow” spike wave discharges. The typical frequency of the spike wave discharges is less than 2.5 Hz, differentiating them from the discharges seen in absence epilepsy (Figure 12.13). At times, these IEDs can appear lateralized, but the lateralization can vary depending on the discharge.

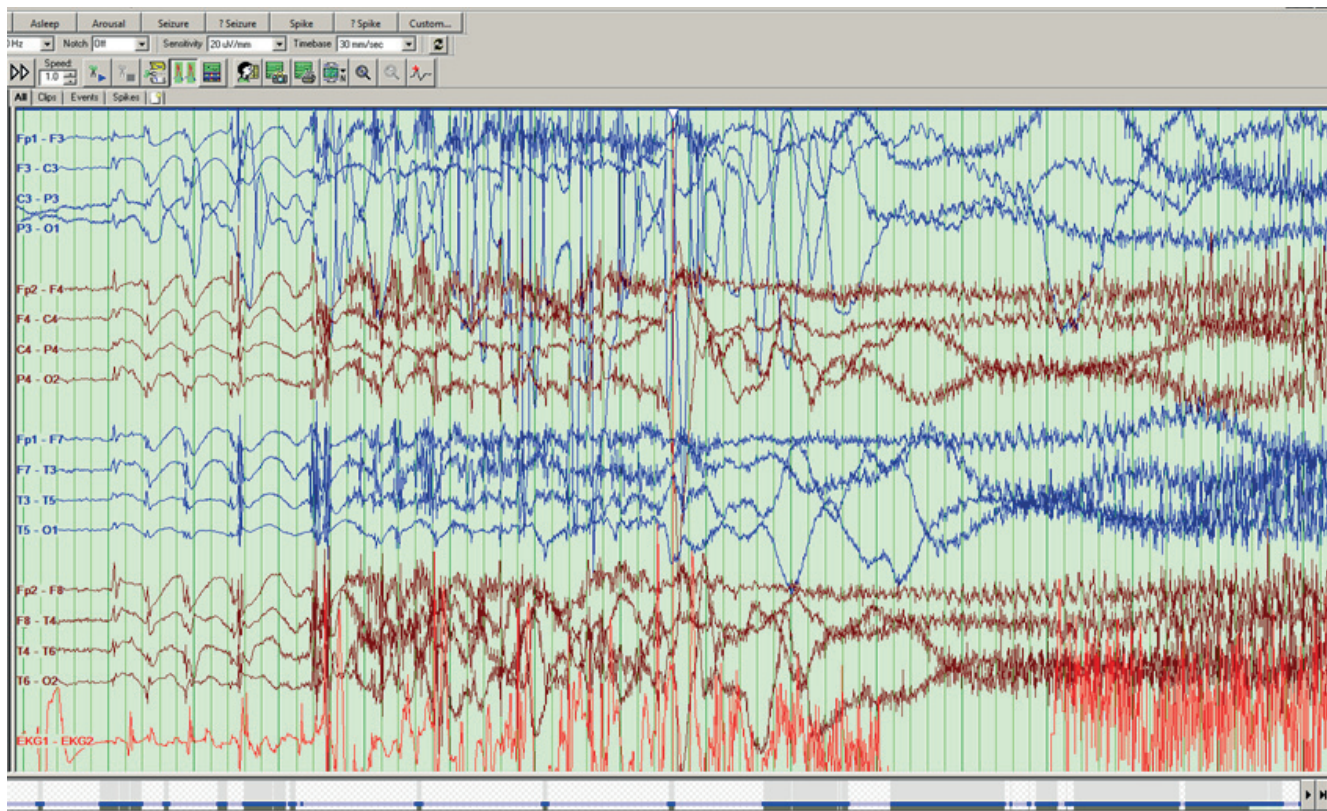
There are several types of seizures that can occur with LGS. Tonic seizures typically manifest as an electrodecrement on the EEG. An electrodecrement consists of suppression of the background activity and appearance of generalized low-amplitude, fast-frequency activity (Figure 12.14). Atypical absence seizures show a long, generalized run of slow spike wave activity, similar to the IED. Drop, or atonic, seizures have similar slow spike wave activity.

### West Syndrome

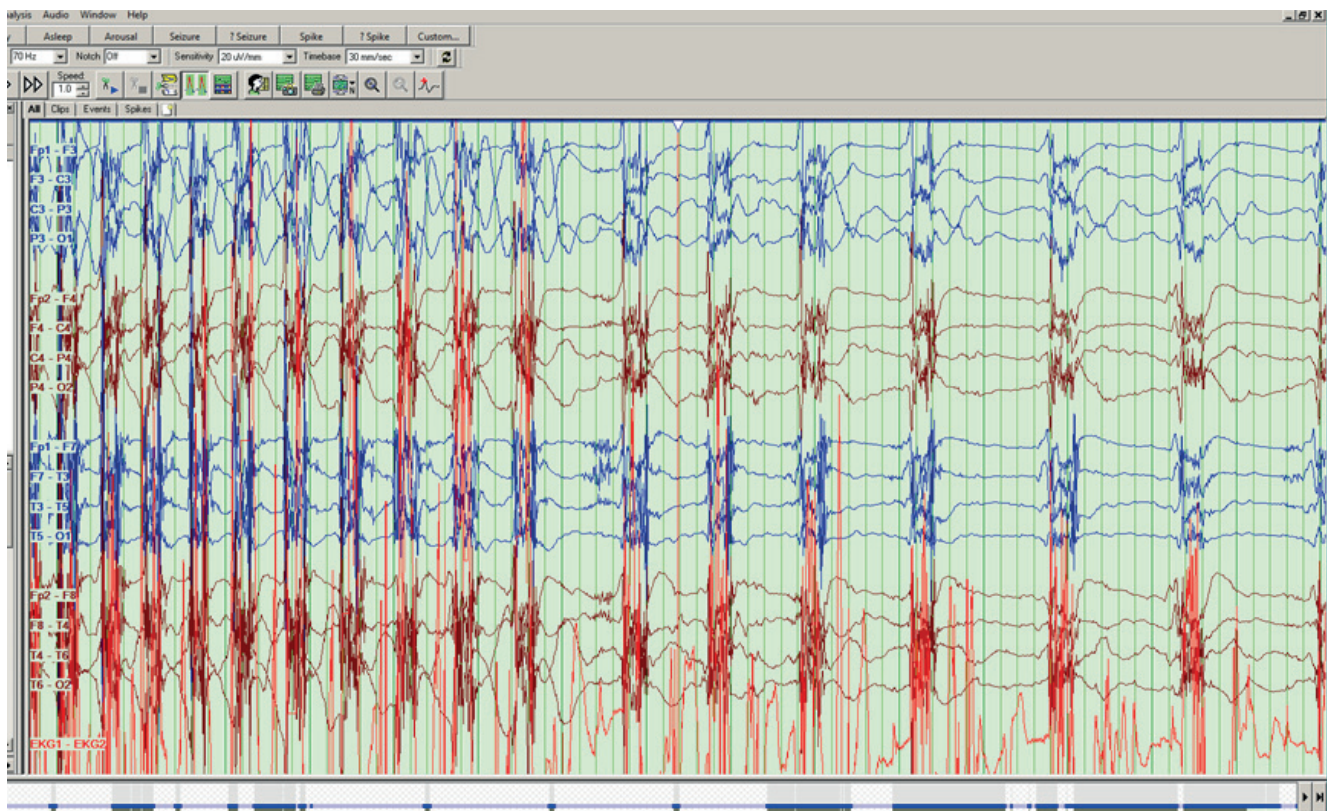
West syndrome is an epilepsy syndrome seen in young children, typically starting in the first year of life. The typical seizures are infantile spasms, and the interictal EEG shows a characteristic chaotic, high-amplitude EEG with multifocal spike and spike wave complexes. This pattern is known as hypsarrhythmia (Figure 12.15). The EEG during the spasms resembles EEG of tonic seizures described earlier (electrodecrement).

Many types of epilepsies have characteristic interictal and ictal findings on EEG. Spikes and sharp waves are commonly thought of as IEDs, but at times rhythmic slow waves can also be epileptiform. Determining the site of origin of the IEDs (focal or generalized) and the dipole orientation of the spikes can greatly help in classifying the epilepsy syndrome. The limitations of EEG in exact localization of the site of origin of the epilepsy should also be appreciated.





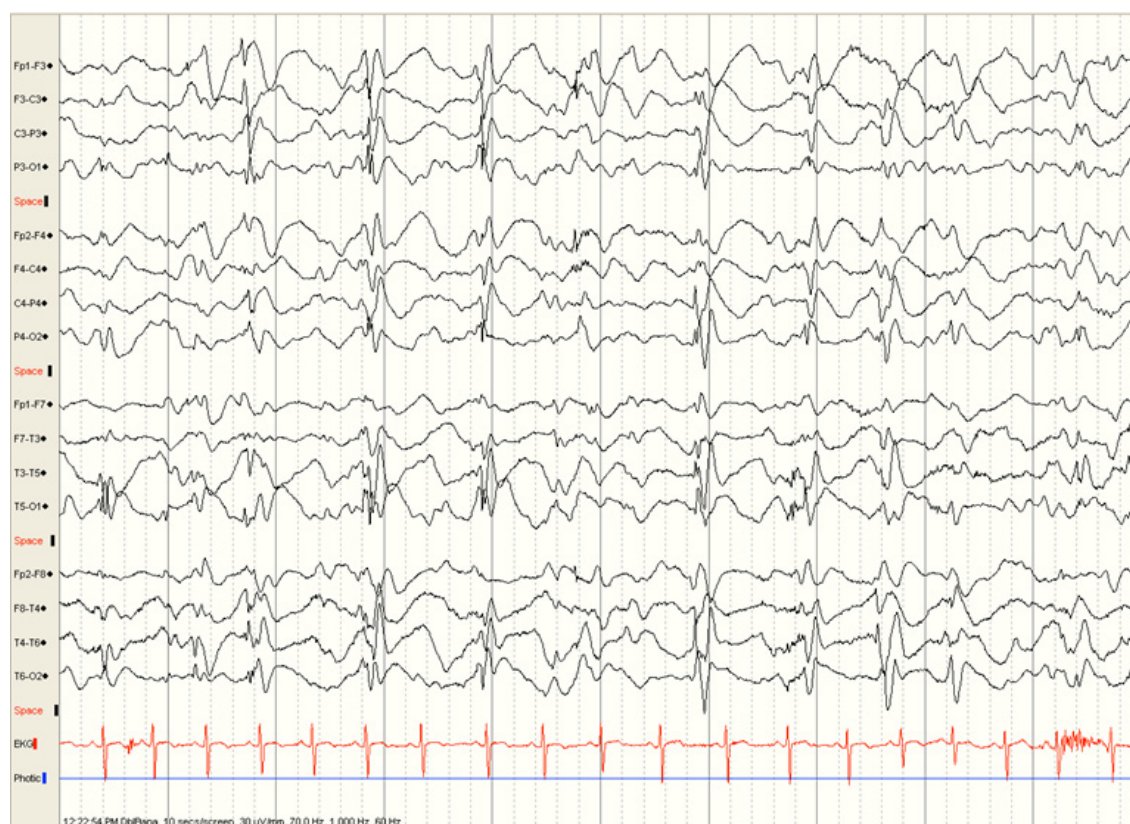
(A)



(B)

**FIGURE 12.12** A generalized seizure shown in a longitudinal bipolar montage in a patient with JME. (A) Shows the onset of the seizure with polyspike wave activity during myoclonic jerks followed by generalized fast activity during the tonic phase. (B) Shows the EEG during the clonic phase of the same seizure.



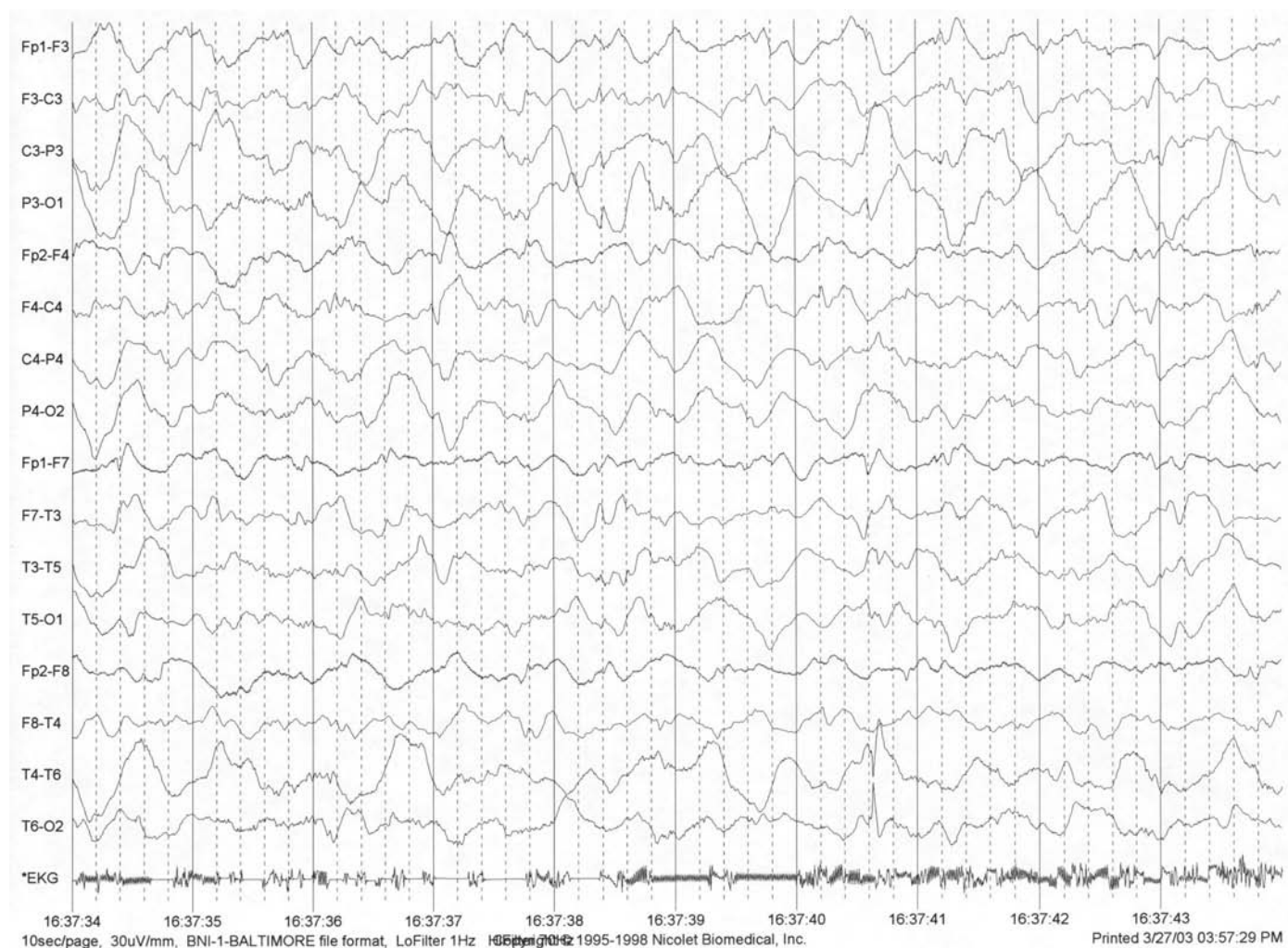


**FIGURE 12.13** This EEG shows a slow spike wave discharge that occurs at a frequency of about 1 Hz. The EEG is shown in a longitudinal bipolar montage.



**FIGURE 12.14** This EEG shows an electrodecrement that commonly accompanies a tonic seizure. Notice the sudden interruption of the background activity by amplitude suppression and fast activity. The EEG is shown in a longitudinal bipolar montage. P4 and O2 electrodes are off.





**FIGURE 12.15** This EEG shows a hypsarrhythmia pattern. Notice that the sensitivity is 30  $\mu\text{V}/\text{mm}$ . Many waveforms are greater than 500  $\mu\text{V}$  and there are multifocal spikes. This EEG is shown in a longitudinal bipolar montage.

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# Ambulatory EEG

*Robbie D. Buechler*

Ambulatory electroencephalography (AEEG) is a monitoring technique that allows the recording of continuous EEG (cEEG) activity when patients are at home. This obviates the need for admission to the hospital for video EEG (vEEG) monitoring in many cases. However, there are situations in which ambulatory EEG monitoring is not adequate, such as in evaluations for surgical treatment of epilepsy. For many other conditions in which spells need to be characterized, this type of monitoring may be sufficient. Details on the background, principles, and importance of EEG in general are described in Chapter 11.

## HISTORICAL PERSPECTIVE

From the humble beginnings and discovery of EEG by German neurologist Hans Berger in 1924, technology and smaller and more high-powered computers have dramatically advanced this field (1). The evolution of EEG into an ambulatory monitoring system first came about via technology put forth by cardiologist, Dr. Holter. Holter was an American biophysicist who invented the Holter monitor, a portable device for continuously monitoring the electrical activity of the heart for 24 hours or more. He donated the rights to his invention to medicine, and his namesake continues on in describing this long-term ECG monitoring system. Soon, buffer delay memory systems based on event monitoring and push button capture of episodes, similar but less sophisticated than ones used for in-patient vEEG monitoring, were incorporated into ambulatory monitoring.

The initial ambulatory system was an EEG preamplifier added to Holter's 4-channel, 24-hour ECG monitoring system. The first person to wear an AEEG did so in Montreal in 1973. In 1982, a 16-channel AEEG system was introduced that utilized signal multiplexing (2). The 16 channels allowed improved spatial resolution and localization, but recorded discrete samples rather than cEEG. In 1983, a cassette tape AEEG system was introduced. It used off-head preamplifiers that had continuous 8-channel recording capability, real-time event markers, and gain and filter adjustments (2,3).

Unfortunately, most of our knowledge about the sensitivity, specificity, and pitfalls of AEEG comes from older, technically limited studies (4). Some of these are detailed later. Renovating this outdated data with up-to-date studies using new more powerful, complex, and even video-containing systems is desperately needed.

In the past decade, computer technology has enabled portable recording of up to 36 channels with sampling rates of up to 400 Hz. Currently, numerous AEEG systems are available commercially. The addition of video monitoring has once again advanced the field and has helped negate one of the biggest disadvantages of AEEG – the lack of visualization of the episodes (5). There is a limited amount of comparative data on the effectiveness of AEEG in contrast to other techniques. This is especially true of newer systems, which have vEEG capabilities.

## TECHNICAL CONSIDERATIONS

Due to the active environment during an AEEG recording, disk electrodes are applied with collodion, the patient's scalp wrapped in gauze, and the lead wires tacked to reduce the chance of disconnection of the electrodes. Examples of commercially available AEEG equipment are shown in Figures 13.1A and B.

Patients are given detailed instructions on recording daily activities and events in a log, as well as in how to use the push-button activation for notable episodes. Though battery life is a concern, with extra batteries, a patient description sheet, and careful demonstration on how to use the equipment, a 72-hour study can be performed without much issue.

Currently available 16- to 36-channel AEEG systems use the similar amplifiers as used for in-patient vEEG monitoring systems, except that many do not have video input. Some also have video capability, but none has the maximal channel (64–128) capability of sophisticated in-patient wired systems. However, these additional channels are not typically needed, as the standard EEG montages are adequate for most uses.



**FIGURE 13.1A** Shoulder harness style-AEEG without video.

New AEEG machines reduce reviewing time by means of sampling (which risks missing infrequent discharges) and automated spike and event detection programs (2).

Despite the progress made with AEEG systems, there remain some technical limitations. Because it is obtained in a very active environment, AEEGs can be fraught with artifacts. Sometimes artifacts can look like electrographic seizures. Electroencephalographic seizures usually “tell a story” with a beginning, evolution with neighborhood/local spread, and an ending, including postictal suppression. Artifacts do not tell such a story. Knowledge and experience can often differentiate true versus artifactual paroxysmal events. Movement, electromyographic, and other types of artifact can also make interpretation of data difficult. Ideally, patient log entries, filtering, and montage selection can ameliorate some of these technical limitations. The data storage limitations of older devices have largely been ameliorated with technological updates to computer processors and ambulatory storage. Archiving of data still needs to be well planned to provide adequate storage, just as in in-patient vEEG monitoring.



**FIGURE 13.1B** Backpack-style AEEG with separate video recorder; wide-angle vEEG one piece systems are also available (not shown).

## APPLICATIONS AND INDICATIONS

The Neurophysiology Subcommittee of the ILAE recommends the use of long-term monitoring where the diagnosis of epilepsy or the classification of the seizure syndrome is difficult to establish (5). This guidance also states that “ambulatory outpatient and community-based long-term monitoring may be used as a substitute for inpatient long-term monitoring in cases where the latter is not cost-effective or feasible or when activation procedures aimed at increasing seizure yield are not indicated.” At this time, there are no specific guidelines or practice parameters for AEEG; however, there are three main reasons why AEEG is performed: a) to characterize behavior events, b) to better define seizure type and epilepsy syndrome, and c) to obtain a longer sample to capture interictal epileptiform discharges (IEDs).

### Behavioral Events

Perhaps the most common reason to perform AEEG is typically when clinical evaluation and baseline EEG are not adequate for diagnosis of epilepsy and if nonepileptic spells are suspected. Objective data are instrumental in the differential diagnosis of epilepsy from psychogenic nonepileptic seizures (PNES), syncope, parasomnias, cardiac arrhythmias, transient ischemic attacks, or other behavioral disturbances.

PNES are the most common type of spell confused with epilepsy. A clinical diagnosis of epilepsy is found to be incorrect in many patients, with many of the incorrectly diagnosed patients having PNES. Many cases of PNES are due to conversion disorder, anxiety, depression, or a combination of these. AEEG may be particularly effective in capturing stress-related PNES as the patient is at home under typical conditions with the usual life stressors. Comparatively, if the monitoring is performed as an in-patient, the typical home stressors are absent, and stress-related spells may be less likely to occur. PNES are discussed in detail elsewhere in this text.

Syncope, particularly convulsive syncope, may be difficult to clinically differentiate from seizures. AEEG has been used in this situation to determine if seizures may be the cause of syncope. Epileptic abnormalities are unusual in patients with syncope, near-syncope, or episodes of dizziness (6). Most syncopal episodes are nonneurological and do not occur with the frequency that allows them to be captured on AEEG.

Nocturnal events have also been studied with AEEG. Sleep is more natural in the home environment than in the hospital, so AEEG is well suited for this determination. Absence of video is somewhat limiting in this situation, but if epileptiform abnormalities are present, the diagnosis is clear. However, the absence of epileptiform abnormalities does not necessarily rule out frontal lobe seizures, and also makes parasomnias a possibility as well.



## Characterization of Seizures and Epilepsy

Even if a diagnosis of epilepsy is clear, AEEG can be helpful in further clarifying seizure type (ie, focal versus generalized) or epilepsy syndrome. In some cases, seizures are considered “intractable” to medications, but, in reality, incorrect AEDs have been used – generalized seizures being treated with medications for focal seizures. Similarly, correct syndromic diagnosis can provide additional information about genetics, prognosis, and treatment that allows more effective treatment.

### Interictal Epileptiform Discharges

A routine EEG is typically 20 to 30 minutes. This is a relatively short window in which to capture transient discharges like IEDs that may help make a diagnosis of epilepsy. With new AEEG systems, EEG data are stored for the entire recording time rather than just during push button alarms or during seizures. The increased EEG sampling time to 48 to 72 hours increases the probability that IEDs will be captured in patients with epilepsy (7). With AEEG studies, natural sleep is captured as well, which also enhances the ability to capture IEDs. Because of these potential advantages in capturing IEDs, AEEGs have been used not only in the diagnosis of epilepsy but also to see if AEDs can be safely withdrawn. Whether AEEG actually helps in making AED withdrawal safer has not been confirmed.

Once recordings extend beyond 72 hours (sometimes even 48 hours), electrode contact starts to deteriorate and artifacts increase. This makes recognizing IEDs more difficult, though electrographic seizures may still be evident. Moreover, combing through a 20- to 30-minute routine EEG for IEDs is commonly done; however, diligently evaluating each page of a 72-hour recording for IED is much more difficult. Automated spike detectors currently lack the sensitivity of seizure detectors, and so they cannot be relied on to identify IEDs.

### Other Indications

There may be other reasons to obtain an AEEG as well. At times, AEEG has been used to determine seizure frequency. This is particularly helpful in situations in which the patient or caregiver is uncertain of the seizure frequency and the provider suspects frequent episodes (8). Alternatively, there may be subtle clinical episodes that are not reliably recognized by the patient and provider. AEEG, especially when combined with video, can help quantify the number of such episodes during the length of the recording. In some situations, AEEG has been used in the evaluation for epilepsy surgery (9). This is not done very often as AEDs cannot be tapered and detailed video analysis is necessary for determination of seizure semiology. In this situation, simply determining that a spell has epileptic correlate is not adequate – the electrographic onset must be determined. If data

quality is compromised, as it often the case later in the AEEG recording, the onset may not be clearly identifiable.

## UTILITY AND COMPARISON TO OTHER TYPES OF STUDIES

A true comparison of AEEG to in-patient vEEG monitoring is difficult due to lack of well-controlled studies using modern-day AEEG equipment. Older studies are limited because they used four to eight channels of AEEG. Some studies evaluate the diagnostic yield by whether IEDs are detected, while others look at the presence of typical spells. Still other studies compare AEEG to a routine EEG. This leaves anecdotal uncontrolled smaller studies and case reports to fill in some of the enormous gaps left by these outdated studies. A recent review nicely summarizes prior studies (7).

In one study in which pediatric patients were evaluated, AEEG was able to capture and determine the nature of spells in 61% of patients undergoing this test for spell characterization (10). For children being evaluated for frequency of IEDs or to better characterize seizure type, AEEG was successful in every case. Another study that prospectively evaluated patients for spell characterization, diagnosis of epilepsy, IED counting, or to determine frequency of seizures, AEEG provided “useful information” in 72% of patients (11). In an adult study in which data were evaluated slightly differently, “positive data” were obtained in 68% of patients (12). Positive data included capturing spells and IEDs. Video recording has been shown to increase the diagnostic yield of AEEGs by 25% to 45%, especially in patients with frequent paroxysmal events (13). Adding video to AEEG, of course, would not be expected to increase utility in cases in which only frequency of IEDs needs to be determined.

Inpatient vEEG monitoring can be inconclusive in determining the nature of spells if the spell is not captured and if IED are not identified. Patients having such nondiagnostic vEEG monitoring studies were discharged with AEEG in one study (14). The diagnostic yield with the AEEG increased by 33% for these patients.

AEEG has shown utility in determining seizure frequency as well. Often patients and caregivers may be unaware of the frequency of seizures, especially when they occur in sleep or when the patient is alone. In one study, patients self-identified only 62% of ictal events with an additional 38% identified by AEEG (8). In 23% of patients, seizures were detected by the program but not recognized by the patient. That is, the patient had a seizure but was not aware of having a seizure. Lack of awareness and underreporting of seizures have significant clinical consequences. A patient’s ability to drive will depend on their ability to recognize their seizures. Individuals with unexplained injuries may benefit from AEEG since it may help identify seizures as the cause of the injuries.

The yield of AEEG in comparison to baseline EEG is considerably higher. Baseline EEG has relatively low sensitivity in detecting IEDs, and often multiple studies must be



done. With AEEG, up to 78% of selected patients had IEDs detected (10). However, in another study of children and adults, IEDs were seen in only 26% of patients, but this still shows an improvement over routine EEG (15). An advantage of AEEG is the diurnal recording. When IEDs occur primarily soon after awakening from sleep, they can be more easily recorded with AEEG than with routine EEG. In one series, almost 5% of 1,000 consecutive patients were noted to have generalized IED soon after awakening from sleep, helping confirm their diagnosis of juvenile myoclonic epilepsy (16).

The duration of AEEG has also been investigated. In one study, 96-hour AEEG assisted with the diagnosis of spells as epileptic or not in 51% of patients (12). Of the events recorded, 58% were recorded within 24 hours and 78% within 48 hours. From these data, 42% and 22% of first events would have been missed if the recording was only for 24 or 48 hours, respectively.

## ADVANTAGES AND DISADVANTAGES

### Advantages

AEEG has many advantages when compared to inpatient vEEG monitoring. Low cost and convenience are probably the biggest advantages. However, there are other benefits as well.

Ambulatory EEG is a cost-effective alternative to inpatient vEEG monitoring in some situations (11). Costs are estimated at 51% to 65% lower than a 24-hour inpatient admission for vEEG monitoring and up to 90% less when monitoring lasts for more than 3 days (16).

The convenience of AEEG is very attractive. Its outpatient nature circumvents the need for hospitalization. Family and caregivers do not need to take time away from their schedules to be with the patient in the hospital. Keeping the patient out of the hospital also does not reduce mobility (which may have other consequences) and prevents exposure to nosocomial infections. For ambulatory patients who are employed or are in school, they may continue going to work or school while undergoing AEEG.

With AEEG, capturing the effects of the patient's natural environment is possible. Various aspects of the environment, such as physical activity, stress, and heat often provoke seizures and spells. These natural spell precipitants often cannot be replicated when the patient is hospitalized. In the home environment, sleep is more natural and not as disrupted as in the hospital. Natural sleep may provoke abnormalities that may help make the diagnosis (17). Recording EEG during the entire natural environmental circadian cycle is useful in capturing spells that occur only at certain times of the day. In addition, circadian variations of IEDs are well documented.

### Disadvantages

Along with the many advantages of AEEG, there are some disadvantages. One of the most significant disadvantages is lack of technologist's support in the nonhospital

environment. Because the patient is ambulatory, the probability that electrodes will be dislodged is high and increases as the duration of recording increases. This can introduce artifacts that may make interpretation impossible. Even if electrodes are not dislodged, desiccation of the gel or paste that enables electrode contact with skin can compromise recording fidelity. Some laboratories circumvent this by having patients return for maintenance of electrodes after 48 to 72 hours. This also allows downloading acquired data and providing the patient with new batteries for the AEEG unit.

Another important limitation is lack of video recording. Absence of video makes determining spell semiology difficult. This raises the issue of whether the spell captured was indeed the patient's typical episode. Sometimes artifacts can mimic electrographic seizures. The presence of video may make this distinction easy, and its absence can raise more questions or lead to misinterpretation. Some newer AEEG units, as noted earlier, have video capability. But even these newer units have a stationary video camera that is usually set in one location. It may not be recording the patient at the moment of the spell, thus defeating its purpose. Nonetheless, having a camera at least increases the odds of capturing the semiology.

One of the common methods of inducing seizures in patients hospitalized for vEEG monitoring is tapering their AEDs. This cannot be done with AEEG. Medication taper may result in a flurry of seizures or tonic-clonic seizures necessitating intervention. This cannot be done in an outpatient, at home setting. This further limits the utility of AEEG.

## FUTURE DIRECTIONS

The utility of AEEG will continue to improve as technology improves. Better battery life and greater storage capacity will allow units to run longer and capture longer samples of EEG. This may require electrode maintenance during the study. Better computer algorithms to detect seizures and IEDs will reduce the human error in identifying epileptic abnormalities. Improved video capabilities may enable better video integration into AEEG machines. Improvements in electrodes may allow for better skin contact and better quality studies. However, what are needed most are high quality studies comparing the utility of AEEG (with and without video) to routine EEG and inpatient vEEG monitoring. This will help practitioners decide which study is most appropriate for their patients.

AEEG is useful to characterize spells, better define a patient's epilepsy, and identify and quantify IEDs. The addition of more channels, digital analysis, and video capability has increased the functionality of this procedure. Artifacts, lack of high-quality video, and inability to reduce AEDs are limitations that have not yet been overcome. However, because of its cost-effective nature and convenience, the use of AEEG will likely continue to increase in the future.

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# ICU Continuous EEG Monitoring

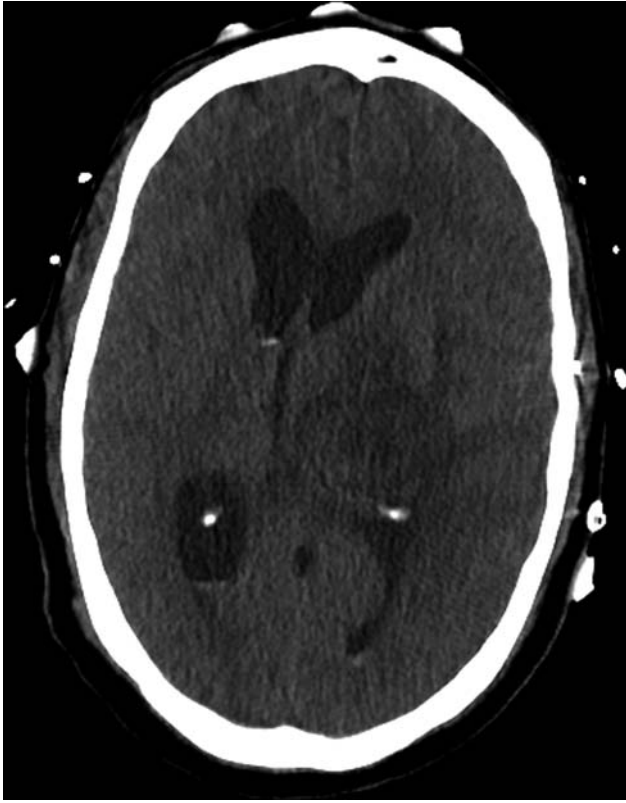
*Keith E. Dombrowski*

The advent of digital video EEG (vEEG) recording has created unique opportunities in the hospital, particularly in the intensive care unit (ICU). Prolonged or continuous EEG (cEEG) monitoring refers to the continuous recording of digital EEG for hours, days, or weeks at a time. cEEG with simultaneous video recording are performed for various reasons but most frequently for seizure monitoring. In the past decade, the role of cEEG monitoring in the ICU has and continues to expand rapidly. Much of this growth has come from the recognition of the high prevalence of nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) in the ICU and growth of neurocritical care services Neuro Intensive Care Unit (NeuroICU) in general. NCS are defined as electrographical seizure activity in the absence of a clear clinical correlate. Status epilepticus has been defined as the presence of frequent NCS, usually occupying more than 30 minutes in an hour of the recording. NCS and NCSE in the ICU were recognized but underappreciated events until late. cEEG is also uniquely suited as a monitor of brain dysfunction in general, particularly abnormal cerebral metabolism. cEEG monitoring is a very sensitive detector of cerebral ischemia and hypoxia, particularly when it is potentially reversible and when clinical examination of the patient is unhelpful or is not possible. cEEG monitoring is suited to the dynamic ICU environment where brain injury can evolve or change quickly. Due to this rapid growth in cEEG monitoring, much more is known about the utility of "ICU EEG," particularly with respect to patient selection and the type and duration of monitoring. However, cEEG monitoring offers many challenges. Clinically, cEEG monitoring in the ICU has presented epileptologists with unique electrographic patterns that can often be difficult to interpret. Logistically, a cEEG monitoring service can be difficult to maintain due to financial, personnel, and technological constraints. However, the future of cEEG monitoring is rapidly becoming a reality with 24/7 availability in most academic centers and real-time interpretation services with some using cutting-edge trending software.

## cEEG MONITORING SERVICE

There are numerous factors to consider when starting or managing a cEEG monitoring service. Digital vEEG has made recording and reviewing hours or days of EEG monitoring possible through high-quality acquisition platforms, efficient data storage, and network accessibility. In the past decade, digital EEG acquisition with a broad dynamic range, excellent noise reduction technology, and high sampling can be easily acquired and reviewed on flexible platforms with intuitive user interfaces. High-definition cameras are routinely used for recording and providing detailed images synchronized with the EEG. The availability of mobile technologies leveraging broadband networks and large-volume digital data storage has made storage and remote review of large amounts of EEG possible. Ever-improving hospital telecommunications and information technology services have been essential in initiating and maintaining such services. Though such services are currently limited to large academic institutions, the price of technology goes down over time and the cost of starting and maintaining such services will become less onerous in the future. Essential components to an effective cEEG monitoring service include a fleet of portable or fixed digital vEEG acquisition systems, a robust network with on-call IT support, and effective data storage and management systems.

Some recent advances in electrode technology have made cEEG monitoring easier to perform and more versatile than in years past. Though reusable gold-plated electrodes remain the norm for many neurophysiology labs, silver-silver/chloride-coated plastic electrodes are more versatile and can reduce the cost of ICU EEG monitoring services (personal communication). Because many patients receiving EEG monitoring have brain injury, the likelihood of needing neuroimaging during a prolonged EEG study is relatively high. Plastic electrodes can significantly reduce the amount artifact seen on CT scans compared to gold-plated electrodes (Figure 14.1). Some electrodes are even employed when



**FIGURE 14.1** Plastic cup electrodes in CT.

obtaining MRI scans as well. This reduces the time and cost of removing and reapplying gold electrodes and will likely improve work flow for a busy clinical service. Needle electrodes were commonly used in ICU and neonatal settings prior to the HIV epidemic. With improvements in needle safety and the availability of disposable needle electrodes, there has been resurgence in their use. Needle electrodes can allow for long-term recordings that provide high-quality data with less maintenance than that of glued cup electrodes. They may also be applied faster than glued cup electrodes, further improving workflow. Though infection and bleeding are a concern, there has been no data to indicate that even long-term needle placement results in a significant risk of infection or injury from placement. As with plastic cup electrodes, needle electrodes can be CT and MRI compatible.

An equal, if not more important, factor to consider is that of staffing, specifically technologists and interpreting personnel. An effective cEEG monitoring service requires 24-hour staffing either with in-house or on-call technologists. Due to the rigors necessary for proper, technically adequate EEG acquisition, registered technologists should be employed whenever possible. The ICU is an electrically hostile environment replete with artifact. Proper EEG electrode placement is necessary to reduce preventable artifacts as well as assist in localization of seizures and other evolving cerebral pathology. Interpreting personnel typically consist

of neurophysiologists or specially trained technologists. In most institutions, cEEG monitoring for seizures consists of continuous recording with intermittent review of the data at various intervals. Unless there is in-house coverage or sufficient networking capabilities, on-demand cEEG review requires 24-hour on-call services and a physical presence in the hospital to review the data. Maintaining a sufficiently large workforce to start and interpret EEG studies is a difficult task for most institutions.

Technological and personnel requirements represent only two hurdles to overcome when operating a cEEG monitoring service. The other significant factor is cost. From one institution, the annual yearly cost of maintaining a busy cEEG monitoring service in 2011 (1500 patient days/year) was estimated at nearly \$460,000, with most of that cost being derived from personnel salaries (personal communication). Cost-effectiveness studies of pharmaceuticals and medical services are becoming increasingly common in the United States and must be considered when determining the true cost benefit of a procedure. Therefore, total cost of a cEEG monitoring service must also consider the hospital charge to the patient and their insurance carrier. Though cEEG monitoring is an expensive service, there appears to be a favorable cost-benefit. One study looked at the outcome of patients with traumatic brain injury and found an improvement in outcome for the patients as well as a significant reduction in length of stay and total cost for hospitalization (1). There are likely other, unmeasurable benefits gained from cEEG monitoring, including discontinuation or reduction in medication and changes in clinical decision making obtained as a result of EEG monitoring. Presently, there are cost-reduction strategies being used throughout the United States to reduce the cost and burden of EEG monitoring as well as improve the accessibility of such services. Such strategies include disposable, nontechnician applied electrode templates or limited electrode arrays for emergency EEG studies. However, further cost-effectiveness studies will be required as cEEG monitoring becomes more commonly employed.

## RECORDING EEG IN THE ICU

The ICU is a very unique environment for recording EEG. There are few places in the hospital where more monitors and equipment are accommodated into a single room. If cEEG monitoring equipment is not “hard-wired,” a portable acquisition system must then be placed in the room as well. Electrical safety of the patient is of supreme importance and ICU rooms are well designed and rigorously tested to ensure that each new piece of equipment can be safely used. However, many other hazards to cEEG monitoring exist. Without adequate training, a study can be disrupted or interrupted by inexperienced staff that may disconnect a network cable, headbox, or video equipment. ICU staff must be properly educated before the introduction of cEEG monitoring in order to reduce the chances of study disruption. Even experienced nurses are significantly challenged when a patient is



placed on cEEG monitoring. They must contend with a large bundle of electrodes, which can become wrapped around IV tubing, bedrails, or other monitoring cables. Without effective management of the hardware, it is easy to accidentally remove even well-secured electrodes. The duration of a cEEG monitoring study also makes degradation of the quality of recording more likely as electrodes may fall or be pulled off in the middle of the night when quick repair is least likely. Transport of a patient on cEEG monitoring is particularly challenging as all cables and wires typically travel with the patient unless they are removed beforehand. Emergent neuroimaging or travel to an operating room may often need to be accomplished with all of the electrodes in place. Most ICUs are supplied with acetone or other solvents. However, in circumstances where the study shouldn't be interrupted, the staff must carefully secure all of the equipment in the bed before transport. Wireless amplifiers may reduce these issues in the future, but these devices are not available in many institutions.

The ICU is also electrically hostile, making unusual artifacts common occurrences. It is essential to know the environment in which the patient is being monitored. Unique artifacts seen during recording include those derived from the ventilator cycling, suctioning, IV drip pumps, bed percussion/vibration modules, dialysis, and aortic balloon pumps/ventricular assistance devices (Figure 14.2). Nursing interventions such as suctioning, chest percussion, and manipulation of the wires are a significant source of artifactual signal. Digital EEG recording offers advantages in mitigating these aberrant signals. Manipulation of montages and filters can assist in eliminating or reducing the impact of environmental and patient-derived artifacts. Most cEEG monitoring machines are equipped with a mechanism to mark or provide notes directly onto the digital record. Annotation of the record by the nursing staff and technologist is very helpful in distinguishing artifact from cerebral signals. Annotations serve an equally useful function of marking when drugs are administered or when movements of interest are noted. As with other forms of prolonged EEG monitoring, the value of simultaneously recorded video cannot be overstated.

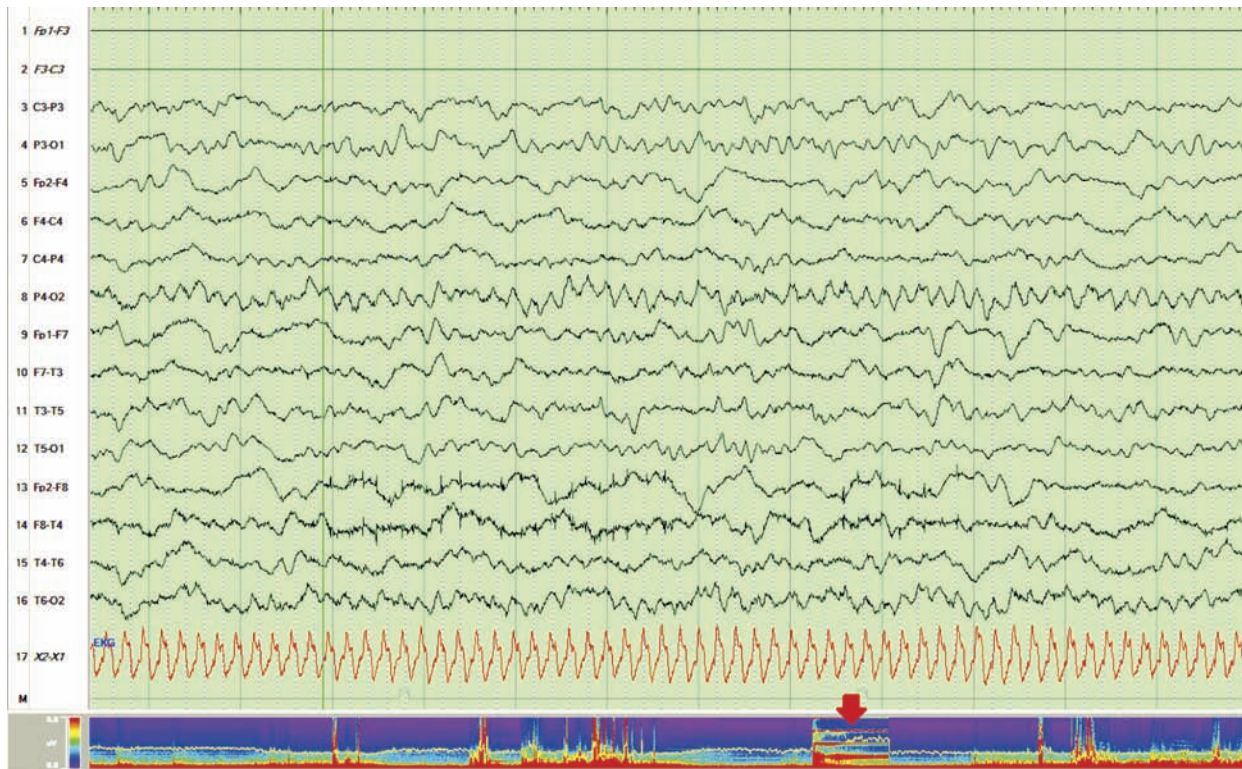
The patient population is as unique as the ICU environment. As many patients requiring cEEG monitoring have significant head or brain injury, technologists must carefully position electrodes to avoid contaminating an open wound or operative site. In many cases, individual electrodes must be displaced or removed altogether. Intracranial anatomy is often shifted due to cerebral edema and intracranial fluid collections, making localization of seizures more challenging. Electrical dipoles may have an aberrant appearance or polarity due to intracerebral hemorrhage or postoperative fluid collections. Head injury often results in significant scalp edema, which can produce attenuation of the EEG signal on the side of the injury. Skulls defects are frequent, making breach rhythms common. Though needles are less frequently used for recording EEG, they present

particular difficulty in patients with large skull defects such as craniectomies. Special consideration should also be given when applying needles in patients with coagulopathies. Patient-generated artifacts are numerous and more common in the ICU, including myoclonic jerking, shivering, asymmetric eye movements, and nystagmus. Knowledge of the patient's admitting diagnosis, skulls defects, and intracranial devices is essential in accurately interpreting the record. It is common for frontal electrodes (F3 and F4) to be missing as a result of an external ventricular drain or other intracranial pressure monitors placed on the skull. In many cases, review of the patient's neuroimaging in conjunction with the EEG can significantly increase the diagnostic yield of the study.

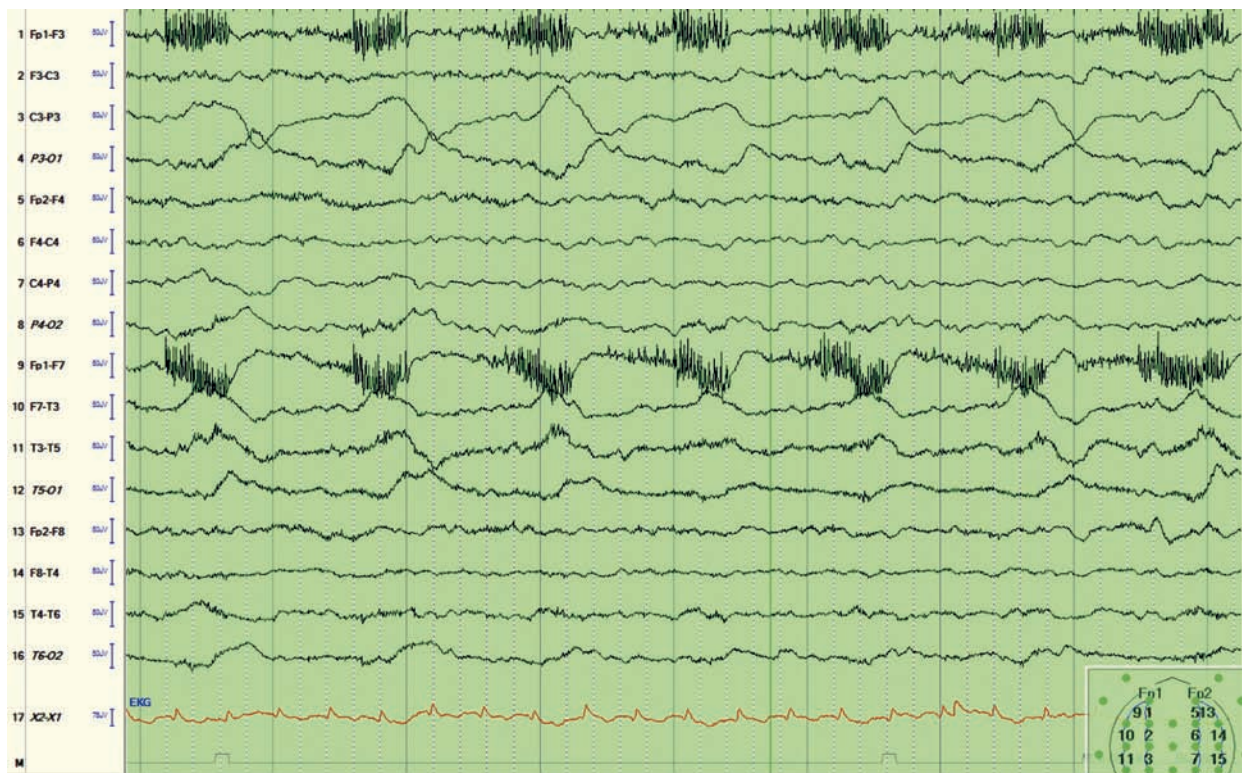
## INDICATIONS

The most common reason for performing a cEEG study in the ICU is for detection of subclinical or nonconvulsive seizures (NCS) in a patient with significant alteration in consciousness. In many cases, cEEG monitoring is initiated after known or suspected clinical status epilepticus. The likelihood of developing subclinical seizures or status epilepticus after GCSE can be over 30% (2). Refractory status epilepticus requires cEEG monitoring for suppression of electrographical seizures. After several important publications, the prevalence of de novo NCS (15%–30%) and NCSE (10%–15%) in the ICU is clearly much higher than previously thought (3,4). cEEG monitoring is the only effective method for detecting these types of seizures and therefore uniquely suited to this job. Early application of cEEG monitoring in the brain injured is critical in identifying and treating NCS and NCSE as seizures become more difficult to treat over time (5). The diagnosis and treatment of NCS and NCSE may be critical in avoiding adverse patient outcomes in certain populations. Though seizure detection is probably the most important question that can be answered, encephalopathic patterns with or without epileptiform abnormalities can provide very useful information. The spectrum of encephalopathic patterns, namely mild-moderate theta slowing, marked and severe delta slowing, suppression, and burst suppression patterns can provide helpful diagnostic and prognostic information for many patients with septic encephalopathy, drug intoxication, and cardiac arrest (CA). In those with suspected but undiagnosed neurological disease, findings of focal slowing and epileptiform abnormalities can provide diagnostic guidance (ie, bilateral independent periodic discharges [BiPDs] in suspected infection, lateralized periodic discharges [LPDs] in those patients with seizures and a leukocytosis). This information can be important for guiding other diagnostic testing.

cEEG monitoring is not limited to the detection of NCS and NCSE and has proven critical in ICU spell characterization. Similar to studies performed outside the ICU, characterization of paroxysmal events is a common use for cEEG monitoring. Stereotyped motor movements presumed to represent seizures are a frequent reason for the request of an EEG or for cEEG



(A)



(B)

**FIGURE 14.2** Examples of artifact in the ICU. (A) Artifact introduced by bed percussion module. The arrow indicates the appearance of this artifact on a compressed spectral array. (B) Artifact introduced by tachypnea on a ventilator. (C) Nystagmus mimicking epileptic discharges in a sedated patient. (continued)



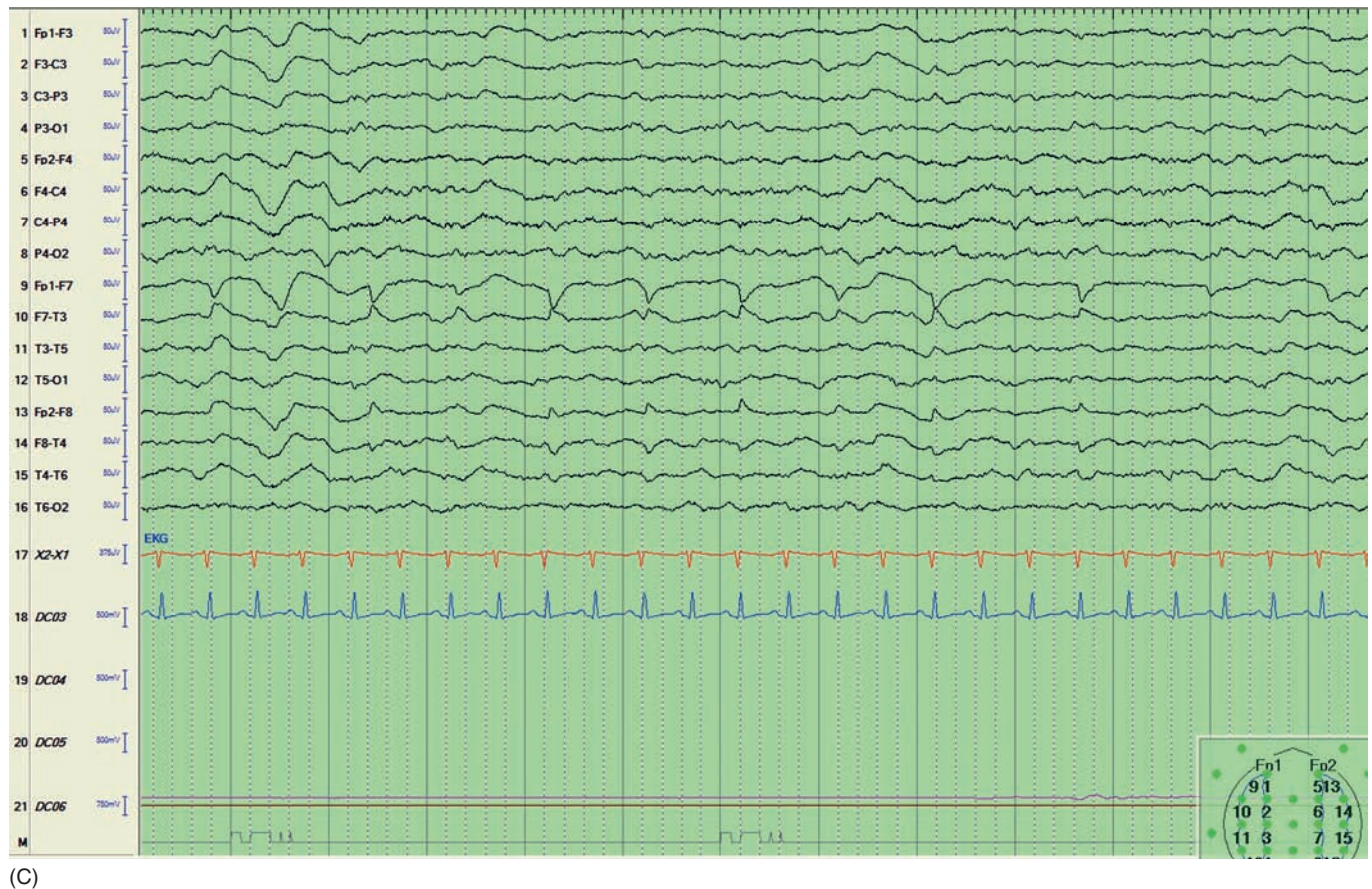


FIGURE 14.2 (Continued)

monitoring in the ICU. Many such movements are seen and include intermittent posturing from herniation, clonus, and tremor. Other more benign movements that are confused with seizure include coughing while on a ventilator as well as stereotyped movements during arousal or emergence from anesthetic agents. In rare circumstances, cEEG monitoring may be necessary to diagnose presumed psychogenic status epilepticus in the emergency room or ICU. Though many stereotyped movements do not represent seizure activity, some very focal seizures may not manifest with a scalp EEG correlate. In other cases, an ictal EEG correlate is obscured by myogenic or movement artifact. Video recording is essential in these scenarios. Alternatively, brief neuromuscular blockade can suppress muscle artifact in order to better visualize cerebral activity that underlies the behavior. This is sometimes necessary in those with frequent myoclonic activity where it is too difficult to differentiate epileptic activity from artifactual signal.

cEEG monitoring is commonly used to measure the depth of anesthesia, whether it is for suppression of seizures or titration to a level of burst suppression sufficient to control intracranial pressure. Though bispectral index (BIS) is frequently used in the operating room, there is limited evidence for its use in those with brain injury. In patients with

refractory status epilepticus, cEEG monitoring is used not simply to monitor for the occurrence of seizure but is also often used to make dose adjustments to midazolam or pentobarbital infusions for burst suppression or complete suppression. Another common indication for dose titration to burst suppression is treating refractory intracranial hypertension. Given the dose-dependent side effects seen with most anesthetics, especially propofol and pentobarbital, complete suppression of EEG activity is often not beneficial if the goal of controlling intracranial pressure has been achieved. In many institutions, pentobarbital remains the agent of choice for controlling refractory intracranial hypertension. As serum levels do not correlate well with either effectiveness or toxicity, cEEG monitoring is required to titrate the effective dose of pentobarbital to obtain burst suppression. Reducing EEG activity to that of burst suppression correlates well with maximal reduction in cerebral metabolic oxygen demand ( $CMRO_2$ ). Avoidance of electrocerebral inactivity (ECI) may reduce the possibility of causing further cardiac suppression. Further dose limiting of barbiturates may decrease the possibility of causing other harmful side effects seen in the ICU, including a gastrointestinal ileus and hypothermia. Though some evidence has suggested that BIS

measurement may be useful in these cases, the standard of care in most institutions remains cEEG monitoring (6).

Routine EEG has been used for several decades as a prognostication tool, particularly after CA. cEEG monitoring is becoming useful for this purpose as well. Though there is no evidence as of yet to suggest that cEEG monitoring would necessarily be more helpful than a routine study for prognostication, consistent and compelling information has been gained from cEEG monitoring. In most patient populations studied, a lack of EEG reactivity in the absence of heavy sedation is consistently associated with a poor prognosis. The evidence for this is best documented in comatose post-CA patients, but it is present in those with TBI and SAH as well. Given the desire for long-term prognostication in comatose CA patients, this form of brain injury has been best studied. Burst suppression patterns with or without therapeutic hypothermia (TH) are associated with a poor outcome, whereas a continuous reactive record is associated with a good outcome (7). Given that TH is now the standard of care and cEEG monitoring is often performed, more prognostic information will likely be available in the future. cEEG monitoring has been useful for prognosis in other conditions including sepsis where the appearance of LPDs is associated with a poor outcome (8). Other forms of EEG abnormalities in sepsis are also associated with a poor outcome, including suppression and triphasic waves (TW, now referred to as PDs with triphasic

morphology). When quantitative trending software is used to analyze a patient's EEG, decreased alpha variability and an increase in delta power is associated with poor outcome in TBI and SAH patients. A decrease in the alpha:delta ratio and an increase in the brain asymmetry index is associated with worse outcome in acute ischemic stroke (7).

A more recent and novel use for cEEG is as a neuromonitor to detect cerebral ischemia alone or as a component of multimodal neuromonitoring. With developments in quantitative EEG trending tools, cEEG monitoring can be an extremely sensitive real-time detector for cerebral ischemia and other forms of acute brain injury, particularly in those patients where the clinical examination is unhelpful. Either alone or in combination with brain tissue oxygen monitors or cerebral microdialysis catheters, cEEG monitoring can provide data on the development or worsening slowing or suppression suggestive of developing ischemia. This is possible through advanced quantitative EEG software packages that trend data in real time. This is an exciting development for cEEG, but this form of monitoring is available in few institutions and requires significant logistical support to be performed reliably and consistently.

An essential part of maintaining a clinical cEEG monitoring service is the development of guidelines or a protocol to foster proper utilization of this service. A truncated example is provided in Table 14.1.

**TABLE 14.1 Duke Guidelines for the Use of Continuous vEEG Monitoring (Truncated)**

<b>Management of Status Epilepticus</b>	
1.	In patients who present in clinical status epilepticus and do not have an improving mental status after treatment, a minimum of a routine EEG should be obtained.
2.	In patients with persistent alteration or fluctuation in mental status 1 to 2 hours after clinical seizures have stopped, continuous EEG monitoring is indicated <ul style="list-style-type: none"> <li>a. If no ictal or interictal abnormalities are noted after 24 hours, cEEG monitoring can be discontinued.</li> <li>b. If seizures or epileptiform abnormalities are seen during the first 24 hours, monitoring should be continued for an additional 24 hours.</li> </ul>
<b>Monitoring for NCSE</b>	
3.	Patients with altered mental status of any cause, particularly those in coma or with a waxing–waning examination, should undergo a minimum of 24 hours of cEEG monitoring. <ul style="list-style-type: none"> <li>a. For those without known neurologic injury, consider extending the monitoring period to 48 hours.</li> </ul>
<b>Monitoring for Seizures following Cardiac Arrest</b>	
1.	cEEG monitoring should be started on all postcardiac arrest patients undergoing therapeutic hypothermia as soon as possible. <ul style="list-style-type: none"> <li>a. Monitoring should continue for 24 hours after normothermia is reached.</li> </ul>
2.	cEEG monitoring should be considered in comatose cardiac arrest patients for up to 48 hours in those who are not undergoing therapeutic hypothermia.
3.	Though there are no data to guide treatment, the presence of ictal activity or status epilepticus should be treated like other types of seizures beginning with phenytoin or levetiracetam, particularly in those receiving therapeutic hypothermia.
4.	Consider somatosensory evoked potentials (SSEPs) within 24 hours of cardiac arrest for any patient who has not regained consciousness within 2 to 3 hours of return of spontaneous circulation.
<b>Monitoring for Seizures in Patients with Traumatic Brain Injury</b>	
1.	All patients with TBI who have a Glasgow Coma Score (GCS) of <9 or fluctuating mental status should receive 24 hours of cEEG monitoring within 24 to 48 hours of admission.
<b>Monitoring of Patients with Subarachnoid Hemorrhage</b>	
1.	For all patients with subarachnoid hemorrhage and a GCS <9, cEEG monitoring is indicated for at least 24 hours.
2.	Currently, monitoring for ischemia from cerebral vasospasm is not indicated.



## DURATION

The duration of ICU EEG monitoring is determined by the indication for the study. Spell characterization, in many instances, can be a short recording as long as the movement of interest has been captured. However, cEEG monitoring may be required for a longer period if there are multiple movements of concern. Monitoring for the detection of ischemia may often be many days during the periods when the patient is at greatest risk for clinical deterioration. For nonconvulsive seizure monitoring, the data are less clear. Owing to limitations in the availability of cEEG monitoring at some hospitals, intermittent routine EEGs may be the only option. However, this is clearly suboptimal and should not be standard practice if cEEG monitoring is available. In both adults and children, the minimum duration of cEEG monitoring for NCS is typically 24 hours. It is unlikely that a single 30-minute or 60-minute study will accurately identify a patient who is experiencing subclinical seizures. However, there are recent data suggesting that EEG studies with epileptiform findings in the first 30 minutes may be more likely to later develop NCS than those without (8). Most seizures, up to 85% to 90%, will be detected when monitoring for 24 hours. The yield may increase to over 95% when monitoring takes place for 48 hours or more (7). Ultimately, the duration of a study aimed at the detection of NCS should be guided by the goals of the monitoring. For those with refractory SE, many days of monitoring may be needed to titrate or taper sedative medications or anticonvulsants to maximal benefit. For those in whom seizures are strongly suspected and the risk of further brain injury is high, the identification of recurrent NCS may be particularly important and require a longer period of monitoring. It is unclear how evolution of existing or further brain injury may affect the propensity to develop NCS. Therefore, it may be wise to monitor a particularly tenuous patient for a longer period of time. Though the detection of NCS or ischemia is an important consideration in critically ill patients, cost-benefit, cost-effectiveness, and resource utilization must be considered. Therefore, monitoring should be ordered when it is indicated but it must be done judiciously. Monitoring strategies that incorporate resource allocation with study indication may be useful in the future (9).

## THE ICTAL-INTERICTAL CONTINUUM

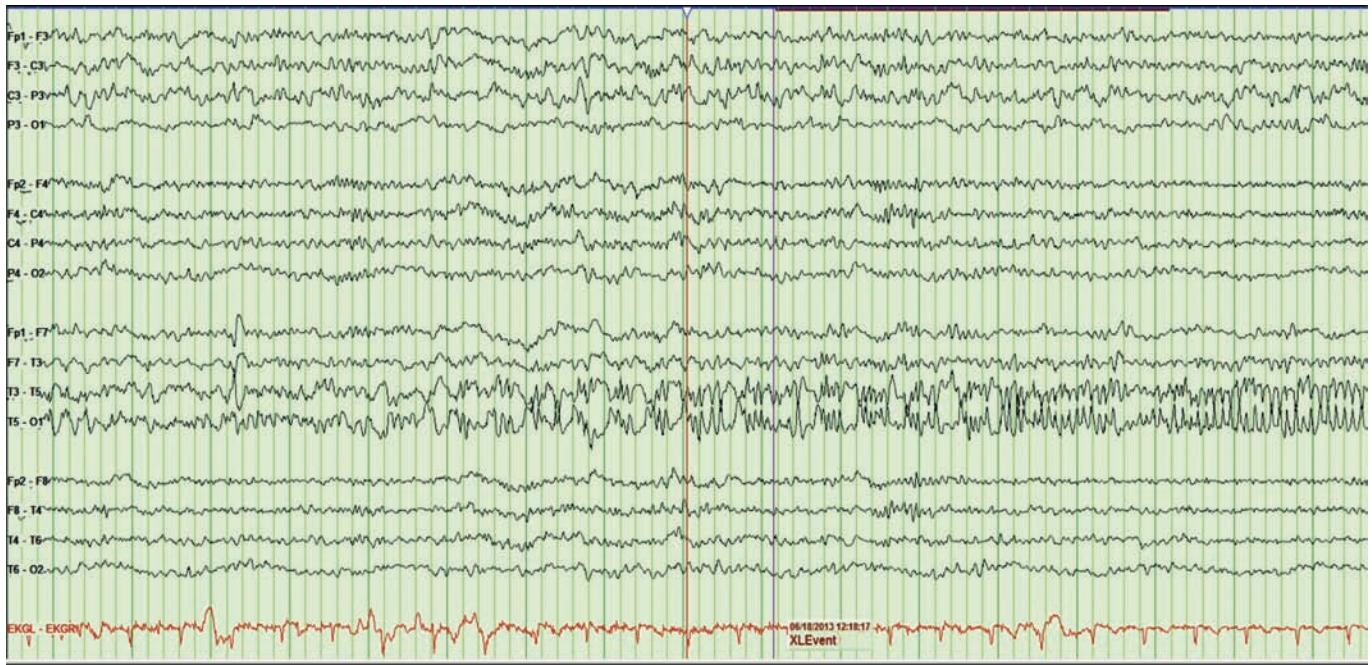
EEG interpretation in critically ill patients can be challenging even after the myriad of artifacts is considered (Figure 14.3). In normal patients undergoing cEEG monitoring, ictal patterns are typically set on normal or near-normal backgrounds that often clearly demarcate ictal from interictal activity. In encephalopathic patients, it is not infrequent to find generalized PDs (GPDs), LPDs, and rhythmic slowing when cEEG monitoring is applied. In some patients, particularly those that are already comatose or profoundly altered, it may be difficult to determine if the pattern seen is ictal, interictal, or nonictal. However, there are some features that

can distinguish more ictal-appearing discharges from those that are more consistent with encephalopathy.

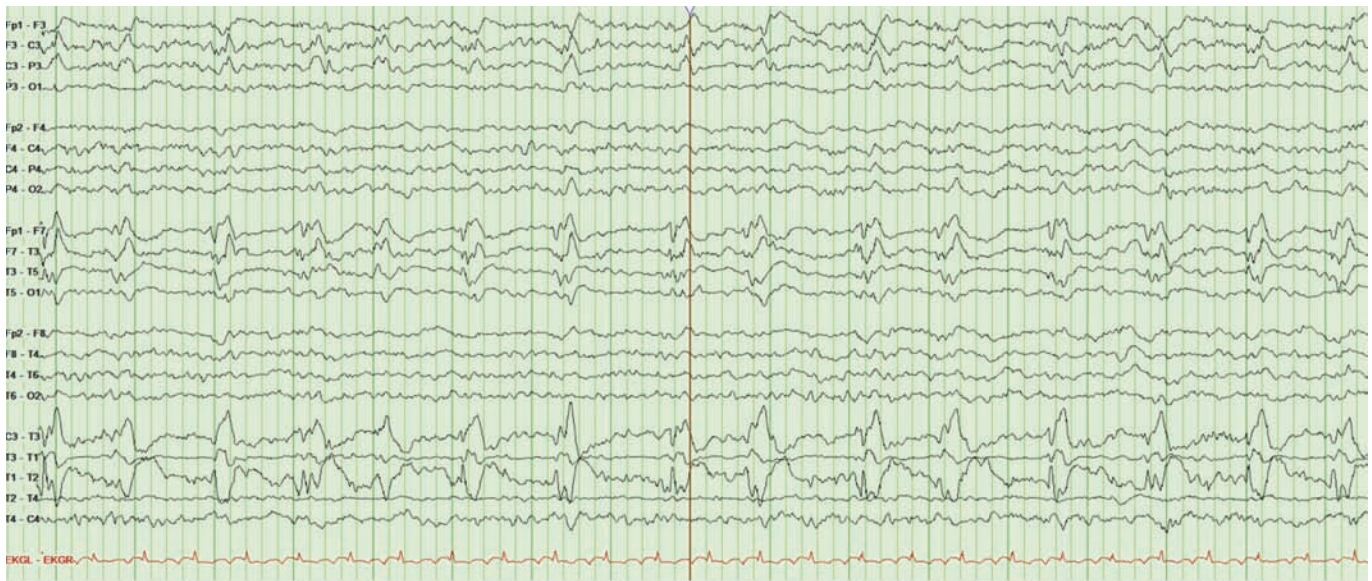
Periodic discharges, whether generalized or lateralized, are a frequent finding and can be seen in severe metabolic encephalopathy, postanoxic encephalopathy, as well as after NCS or NCSE. Though it is difficult to discern which are “peri-ictal,” those that occur in the setting of a low-amplitude background are sharper or more “spiky” and of higher amplitude are more likely to be related to seizure than encephalopathy. Similarly, GPDs with superimposed fast activity or those that are polyphasic are more likely to represent an ictal pattern. Similar concerns arise when PLEDs are seen. In unusual circumstances, LPDs are associated with a clinical correlate such as muscle twitching and are likely ictal. In such cases and others where LPDs are suspected to be ictal, the discharges are likely to be polyphasic or complex with superimposed fast activity (LPDs+F). The frequency of the periodic activity may also vary significantly during the course of the recording. The significance of this unknown and determination of the ictal or nonictal nature of this activity must be determined individually. On the other hand, monomorphic or “proper LPDs” (or simply LPDs) with a nearly fixed frequency are generally considered interictal or nonictal if accompanied by known neuronal damage. Though some LPDs may be judged nonictal, they are highly associated with the occurrence of seizures and treatment should be considered in most cases.

Triphasic waves (TW) are another pattern of great debate. For many years, this pattern has had a certain etiological significance attached to it, specifically hepatic encephalopathy. Years of experience summarized in recent publications have shown that TW are frequently seen in conditions other than liver disease. TW can be seen as an interictal pattern, after anoxic injury, and in many cases of metabolic encephalopathy including renal disease and other toxic encephalopathies. Similarly, the morphology of TW is highly variable and often does not have all of the defined features such as anteroposterior lag or frontal predominance. In all of these cases, the morphology of the discharges will often change during the course of a recording from less sharp and benign appearing to sharper and more ictal appearing. The significance of these changes is unknown and will need to be considered individually.

Interesting phenomena that have received a great deal of attention in recent years are stimulus-induced rhythmic, periodic, or ictal discharges (SIRPID). SIRPID are commonly seen and appear to represent another pattern on the ictal-interictal continuum. SIRPIDs are epileptiform or rhythmic discharges consistently induced by arousal of critically ill obtunded or comatose patients. In many circumstances, the discharges have an evolution suggestive of an electrographic seizure. At other times, arousal produces periodic discharges or rhythmic patterns such as frontal rhythmic delta or combinations of different patterns. The SIRPID pattern can vary significantly between- and within-individual patients during the course of an EEG recording. The relationship of SIRPIDs to clear electrographic seizures is unclear as is the potential to produce neuronal injury. They are seen in



(A)



(B)

**FIGURE 14.3** Unique ICU EEG patterns. (A) High-frequency seizure seen in the setting of breach artifact in a patient with extensive edema from a tumor. (B) Lateralized periodic discharges with fast activity (LPDs+F) using the proposed ACNS ICU EEG terminology. These discharges were seen in a patient with intermittent seizure activity in the setting of a high-grade brain tumor.

many critically ill patients, but there is poor correlation to those patients who had electrographic seizures prior to or after the appearance of these SIRPIDS. SIRPIDS were more likely to be seen after status epilepticus in one study (10). Although the true pathologic potential of these patterns is unclear, SIRPIDS are frequently treated with antiepileptic drugs (AEDs) by many providers.

In cases where it is unclear if a pattern is ictal or not, a benzodiazepine challenge can be useful. This bedside test

is performed by administering increasing low doses of a short-acting benzodiazepine such as midazolam and observing for a clear change in the EEG and a clinical response by the patient. Low doses of benzodiazepine reduce the chances of respiratory depression or hypotension. However, this test must be performed in a monitored clinical setting to prevent significant adverse events like acute respiratory failure and hypotension. As an example, an encephalopathic patient with LPDs+F is administered sequential doses



of 1 mg of midazolam with a clinical and EEG assessment between each dose. The test is considered positive if the EEG improves (concerning patterns resolves or normal patterns appear) and the clinical examination improves. The test should be considered equivocal if the EEG improves but the patient does not. Though prompt clinical improvement can be seen, it should be expected that some patients with severe neurologic illness will take several hours to return to their baseline or begin following commands. Any expected clinical improvement should be based on their pre-EEG state. Though the benzodiazepine challenge can be useful, the true reliability of this test is unknown.

Without further studies, the true pathological significance of these patterns and discharges will likely remain a mystery for the foreseeable future. To combat some of the confusion, the American Clinical Neurophysiology Society has embarked on an effort to create standardized language by which to interpret cEEG monitoring data (Table 14.2). Although the true significance of the newly defined waveforms is unknown, standardizing language will not only facilitate communication but will also help define the clinical significance of many of the EEG patterns seen in the ICU.

## QUANTITATIVE EEG

Quantitative EEG (QEEG) is a general term used to describe methods of EEG analysis using mathematical formulas and statistical analysis. Raw EEG data are transformed or compressed in time, frequency, joint time–frequency, and time–amplitude domain graphs and spectra to facilitate the display of long periods of data. Many of the methods consist of linear mathematical analysis. More advanced nonlinear methods (ie. entropy) are now also being used in clinical practice to facilitate detection of seizures and characterize other clinically relevant disease states such as global cerebral anoxia and cerebral ischemia. These data are incorporated into different tools including event detectors and topographic source analysis to alert an EEG reviewer to a particular event and localize the findings. Changes indicative of seizure, ischemia, or expanding mass lesions are then accentuated in ways that would be difficult to discern from the raw EEG. Although QEEG has been available for a few decades, the evolution of digital EEG has made its application far easier and more clinically relevant. Numerous QEEG software packages are currently commercially available and in use at institutions around the United States, including that created by the Persyst corporation (San Diego, CA), which is one of the most widely used systems. Other QEEG software packages available for use in the ICU include those made by Moberg Research (Media, PA) and those included with many of the major EEG vendors' software. Continuous data review is being increasingly emphasized in ICU cEEG monitoring and QEEG will likely be an integral component in accomplishing this goal. Due to limited numbers of trained clinical neurophysiologists, training of technologists or ancillary personnel to review QEEG data will be essential. Therefore, an easily interpreted user interface is critical. Most QEEG packages

**TABLE 14.2 ACNS Critical Care EEG Terminology Adapted from ACNS Guidelines 2012**

### A. Rhythmic or Periodic Patterns

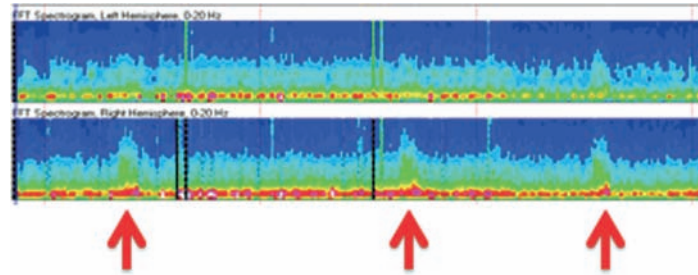
1. Main Term 1:
  - a. Generalized (G)
    - i. Any bilateral, bisynchronous, and symmetric pattern.
    - ii. Pattern could be frontal, occipital, and midline predominant or generalized, not otherwise specified.
  - b. Lateralized (L)
    - i. Any unilateral or bilateral synchronous but asymmetric pattern including focal, regional, or hemispheric patterns
  - c. Bilateral Independent (BI)
    - i. Refers to the presence of three independent lateralized patterns.
  - d. Multifocal (MF)
    - i. Refers to presence of at least three independent lateralized patterns with at least one in each hemisphere
2. Main Term 2:
  - a. Periodic Discharges (PDs)
    - i. Periodic is defined as repetitive waveform with relatively uniform morphology and duration with quantifiable interdischarge interval between consecutive waveforms at fairly regular intervals.
    - ii. Discharge is defined as waveforms with no more than three phases or any waveform lasting 0.5 seconds or less, regardless of the number of phases.
  - b. Rhythmic Delta Activity (RDA)
    - i. Rhythmic is defined as a repetitive waveform with relatively uniform morphology and duration and without an interval between consecutive waveforms.
  - c. Spike-and-wave or Sharp-and-wave
    - i. Spike, polyspike, or sharp wave followed by a slow wave in a regularly repeating and alternating pattern with a consistent relationship between the sharp/spike and wave components. No interval should be present between one complex and the next.
3. Modifiers
  - a. Modifiers are provided for the prevalence, duration, frequency, number of phases, sharpness, amplitude, polarity, and whether the pattern is stimulus-induced or evolving and fluctuating.

display multiple trends simultaneously to facilitate interpretation of seizures and cerebral ischemia (Figure 14.4).

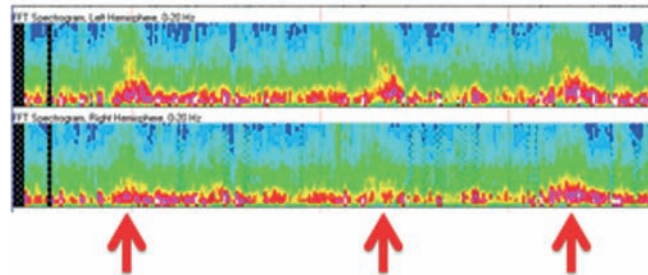
QEEG analysis has been used to a different degree in various disease states and clinical environments. The tools that have garnered the greatest amount of attention and study include various frequency analyses performed with fast Fourier transformation (FFT). This mathematical formula can perform wave subgroup analysis and display the data as spectral arrays or graphs that can be trended. Similarly, power analysis of different frequencies or ratios can be performed. Such QEEG trends have undergone extensive study to determine their utility in seizure detection. The simplest quantitative trend is a compressed spectral array (CSA) or color density spectral array (CDSA). These trends can be applied to select regions, individual hemispheres, or the entire electrode array. Though the display and input electrodes will vary between QEEG montage, a typical CSA

## Example seizures on FFT

Example 1.



Example 2.

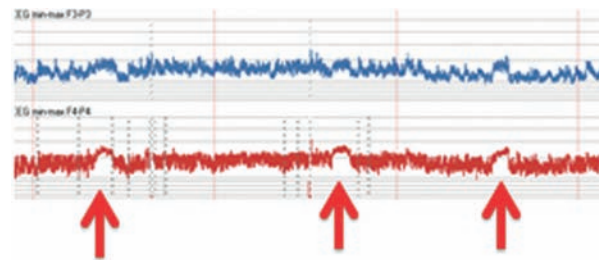


(A)

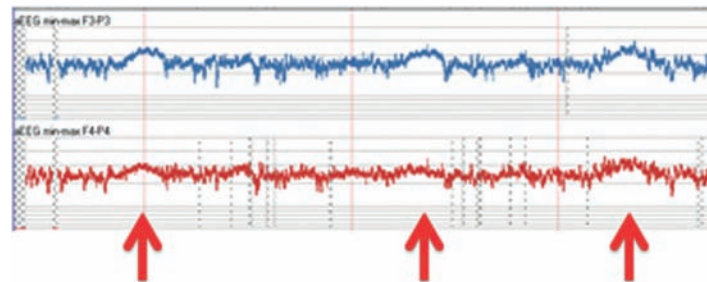
## Example seizures on aEEG

Seizures are typically seen as an increase in amplitude of the aEEG

Example 1.



Example 2.

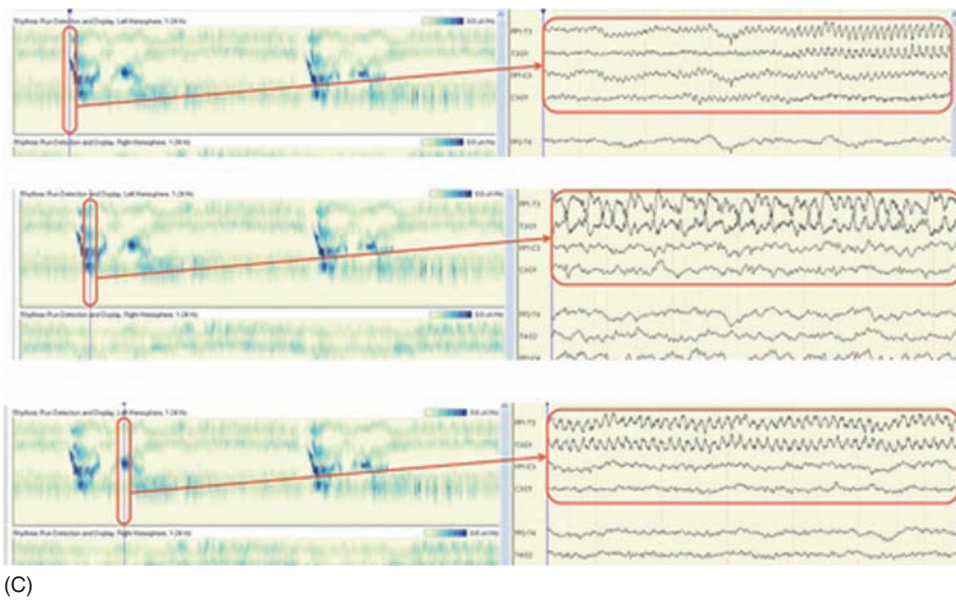


(B)

**FIGURE 14.4** Examples of different QEEG calculations for seizure activity and artifact. Duration of each QEEG block is 1 hour. Red arrows indicate individual seizures. (A) Seizure activity as it appears using a compressed frequency spectrogram. (B) Seizure activity as it appears using amplitude integrated EEG (aEEG). (C) Seizure activity as it appears using the R2D2 display of the Persyst™ software. (D) A typical seizure detection panel using Persyst™ software with R2D2, FFT spectrogram, asymmetry index, and aEEG panels. (E) Bed percussion artifact as it appears on a seizure detection panel. (continued)



## Anatomy of a seizure on R2D2



## Persyst seizure detection panel

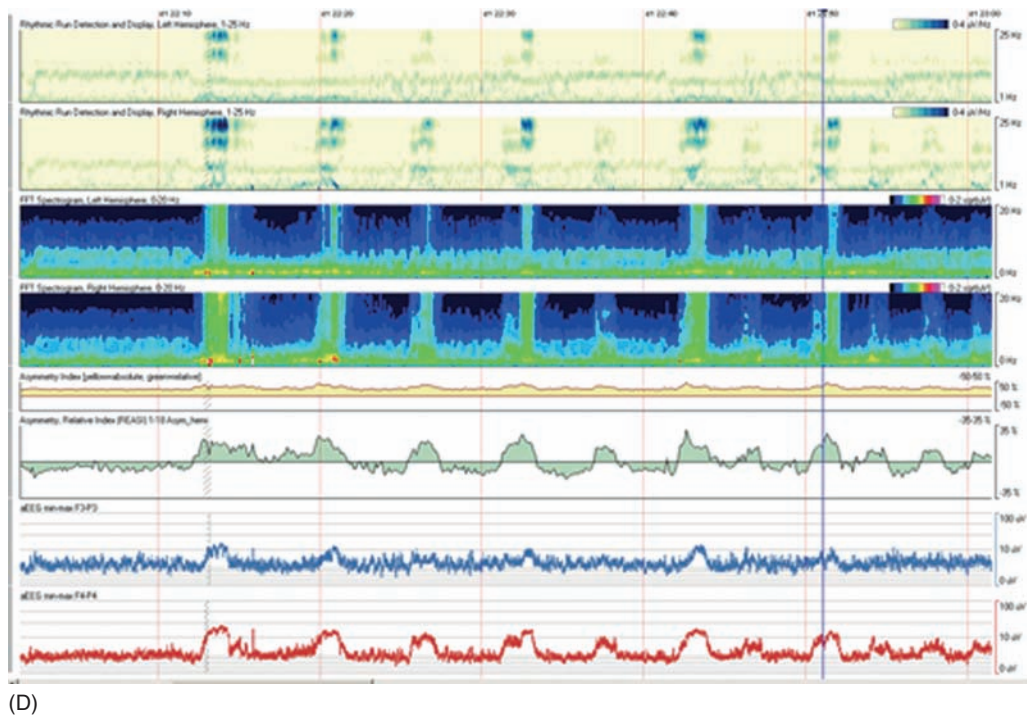


FIGURE 14.4 (Continued)

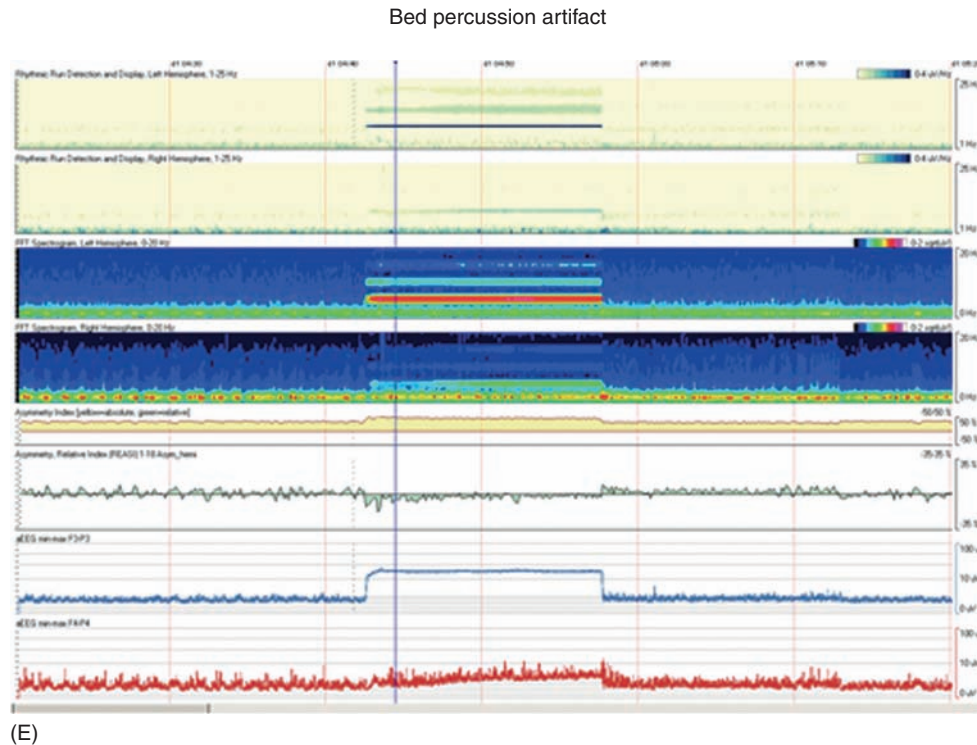


FIGURE 14.4 (Continued)

or CDSA will display a differential color scheme of frequency power generally up to 20 Hz. With minimal training, interpreters can examine hours of compressed EEG on the CSA for patterns that appear consistent with seizure activity (Figure 14.4A). Although a false negative detection of approximately 10% should be expected, CSA and other FFT frequency spectrograms have proven useful in facilitating seizure detection and rapid review of cEEG monitoring studies (11). QEEG using FFT has also been leveraged for cerebral ischemia detection. Numerous indices, typically composed of a ratio of fast and slow frequencies (alpha:delta ratio, relative alpha and delta percentage), have been helpful in detecting cerebral ischemia hours and sometimes days before its development (12). Ischemia detection using QEEG has been most useful in patients with subarachnoid hemorrhage as well as acute stroke and carotid endarterectomy.

Amplitude-integrated EEG (aEEG) has also garnered a great deal of attention in monitoring pediatric and adult ICU patients. The aEEG is commonly utilized in neonatal populations to monitor cerebral function. The aEEG displays show a time-compressed EEG amplitude signal on a semi-logarithmic scale. Similar to FFT frequency trends, aEEG has been useful for seizure detection as well as for monitoring comatose patients or maturity level in premature neonates. Rhythmic activity and seizures can be seen with an increase in activity in the lower margin of the aEEG monitoring trend. As with FFT, aEEG is subject to numerous artifacts that can confound interpretation. Seizure detection can be difficult in

those seizures that are brief or those that are of low amplitude (11). As with FFT, review of the raw EEG is necessary to confirm the presence of seizure activity.

As software becomes more sophisticated, newer QEEG algorithms are being tested or have recently been incorporated in clinical practice. A great deal of effort has been placed on novel seizure detection algorithms in addition to the traditional QEEG trends. Examples of these include proprietary seizure probability indices and rhythm detectors such as the Persyst rhythmic run detection and display trend (R2D2). This FFT-based trend highlights those frequency spectra that display rhythmic activity. One pitfall of most traditional seizure detectors has been a failure to accurately interpret many of the seizures that are observed in the critically ill. Seizure patterns and evolution are frequently very different from those recorded in an epilepsy monitoring unit and seizure probability scores may not be as accurate in the ICU. Therefore, more advanced algorithms are being developed, including those with waveform recognition and neural network capabilities that facilitate algorithm “learning.” Similarly, more advanced nonlinear mathematic calculations, such as entropy, are also being used to better define the EEG of brain injury. Though time-frequency analysis has been very useful, it is less suitable for analyzing unpredictable EEG patterns resulting from brain injury such as hypoxic injury (13).

Although QEEG has advanced significantly in recent years, artifact detection and rejection has been a central criticism of these programs. It is not uncommon for many

artifactual signals to mimic seizure activity including bed percussion modules, coughing, and myogenic artifact. Similarly, asymmetry indices will be difficult to follow in a patient with a skull defect and breach rhythm. Significant effort has been made to identify and reject these signals on the final QEEG output. Current software packages and systems are now being designed with automated artifact rejection algorithms to combat this issue. However, even very advanced artifact rejection algorithms will not replace the need for intermittent review of the raw EEG to confirm the presence or absence of electrographic seizures.

There have been remarkable advances in cEEG monitoring in the past two decades. As the frequency of NCS and NCSE in comatose ICU patients has been realized, the use of cEEG monitoring has grown. This has resulted in many challenges, including resource utilization. However, it has also provided many opportunities for further research, such as determination of the significance of various EEG patterns in critically ill patients. Advances in QEEG have the potential for revamping how and who reviews the cEEG monitoring data. This is a field that will certainly continue to evolve rapidly.

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# Epilepsy Surgery Evaluation

*Tung T. Tran*

## 15

C H A P T E R

Consideration of epilepsy surgery is important in the treatment of patients with persistent epileptic seizures despite optimal medication management. About half of all patients with epilepsy will have successful seizure control with their first appropriately chosen and well-tolerated antiepileptic drug (AED). Another 10% to 15% will find success with a second appropriate AED. Unfortunately, after two good AED trials, less than 5% will achieve success with the addition of more medications (1). Those patients whose seizures are not well controlled despite multiple trials of AEDs, traditionally referred to as having intractable epilepsy, are also described as having drug-resistant epilepsy (DRE). The International League Against Epilepsy's (ILAE) definition of DRE is "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (2). Risk factors for DRE include poor response to the first AED and signs of higher epilepsy burden, including frequent seizures, a long duration of epilepsy, and a history of status epilepticus.

There are multiple reasons why a patient treated with AEDs continues to have seizures. One of them is the aforementioned DRE. The others are inappropriate or poorly tolerated AED treatment and misdiagnosis. In any of these cases, if seizures are not controlled, the patient should be referred to an epilepsy specialist. Diagnostic tests, such as an epilepsy monitoring unit (EMU) admission, may have great impact on a patient's quality of life. Before a patient has any sort of surgical intervention, their seizures must be thoroughly evaluated.

Partial seizures are generally more difficult to control with medications when compared to idiopathic generalized epilepsy. Fortunately, partial seizures are sometimes amenable to surgical resections, while generalized seizures are not. The majority of this chapter describes the use of surgical resection for partial seizures. However, there are surgical treatment options for generalized seizures, including corpus callosotomies and vagus nerve stimulators, to be discussed in Chapters 30 and 31. Callosotomies, in particular, can be very useful for patients who fall and injure themselves.

These patients often require helmets because of the severity of their falls. A callosotomy can reduce the injuries and falls, if not necessarily the seizures. Therefore, an epilepsy center evaluation should be considered for all patients with any persistent debilitating seizures.

### REFERRAL FOR EPILEPSY SURGERY

All patients with debilitating partial seizures and DRE should be referred for epilepsy surgery work-up because DRE implies life-long impairments. In these patients, epilepsy surgery may offer a possible cure. The goal of any patient with epilepsy is "no seizures, no side effects."

### Benefits

Patients with DRE may have a multitude of complications. Persistent seizures mean increased risk of injuries from falls. Quality of life is often affected because driving, employment, social isolation, and stigma may be associated with intractable seizures. The continued use of AEDs may cause cognitive and mood impairments, as well as other long-term side effects associated with chronic medication use, such as impaired bone health. DRE patients are often on multiple medications, which can lead to toxicity effects. Furthermore, persistent seizures are related to increased mortality, whether due to status epilepticus or sudden unexpected death. These topics are discussed in chapters located in Part IV of this book and are the emphasis and motivation behind controlling seizures. This is especially important because many patients with DRE can potentially be cured.

While surgery is often considered by patients and practitioners as a drastic measure, studies show that, for select DRE patients, the long-term benefits and tolerability of surgery are significantly better than prolonged unsuccessful treatment of DRE with AEDs. About two out of every three patients who undergo temporal lobe resections become seizure-free, with an additional percentage having significant decrease in their seizure frequency. Many of these patients,

after surgery, can drive, work, and live lives relatively free from the persistent fear that a seizure can occur at any time. Furthermore, some are weaned off of all seizure medications. These patients avoid the long-term side effects of chronic AED use. Also, from an economic standpoint, the up-front cost of surgery is much cheaper than the cost of years of medications, emergency room visits, and loss of productive time.

Additional advantages of epilepsy surgery will be discussed in a later section on positive outcomes, including the persistent improvements in quality of life. The number of patients with drug-resistant temporal lobe epilepsy one needs to treat with epilepsy surgery before demonstrating an advantage over conservative treatment is only two (3). This demonstrates the high effectiveness of epilepsy surgery and why it is considered the standard of care for patients with DRE.

### Whom to Refer

The American Academy of Neurology (AAN) Clinical Practice Guidelines states that any patient with disabling complex partial seizures who has failed appropriate AED treatment be considered for epilepsy surgery referral (4). In fact, anyone who continues to have partial seizures that affect their quality of life, despite their practitioner's best efforts, should be offered an evaluation for possible surgery. This may include those patients with only simple partial seizures, as frequent auras can sometimes have an impact on a person's life. Similarly, even one major seizure, however rare, can cause significant injury if occurring at an inopportune time. Thus, there is no minimal criterion for seizure intensity or frequency with regard to epilepsy surgery, as long as their epilepsy continues to have a negative impact on a patient's life.

Furthermore, referrals to epilepsy centers are not restricted by seizure type. While surgical resection is restricted to patients with partial seizures, there are other advanced techniques, discussed in Part III of this book, which may be very helpful. Also, sometimes secondarily generalized partial seizures may mimic primary generalized seizures. Prolonged video electroencephalography (vEEG) monitoring may help differentiate between the two. If a practitioner is unable to satisfactorily control seizures, that is enough reason for an epilepsy center referral.

The Canadian Appropriateness Study of Epilepsy Surgery (CASES) group has placed a free, simplified questionnaire online at [www.epilepsycases.com](http://www.epilepsycases.com) to evaluate the appropriateness of epilepsy surgery referral. It is based on seizure characteristics such as type, severity, frequency, and first onset, along with treatment success, side effects, and prior diagnostic results.

For the purpose of encouraging patients to be seen at an epilepsy center, it may be helpful to know that certain characteristics correlate with patients having better outcomes with surgery. One is the identification of a focal brain lesion.

Concordant imaging and EEG suggest a higher chance of seizure freedom after surgery. That said, sometimes lesions are not identified initially. With additional work-up, however, surgery can often be successfully performed when a lesion was not initially seen (5). Therefore, the absence of a focal brain lesion should not prevent one from being referred to an epilepsy center.

Other factors influence success of surgery. Along with imaging abnormalities, EEG abnormalities correlate to more positive outcomes. This suggests that better localization of epileptogenic regions lead to better results. On the other hand, not surprisingly, more severe preoperative seizures relate to worse outcomes. Patients with secondarily generalized seizures have relatively reduced remission rates than those without. Patients with lower IQ and comorbid psychiatric disease are also thought to have higher seizure recurrence rates after surgery. Another important predictor of surgery success is duration since the time of onset, with longer durations having worse outcomes. However, no one poor outcome risk factor necessarily precludes a patient from getting an epilepsy surgery evaluation.

### When to Refer

If someone with DRE is a good surgical candidate, they should be referred for epilepsy surgery as soon as possible. In any case, after two appropriate AED treatment trials, there is little evidence that postponing surgery is helpful. Some patients with DRE may go months without a seizure, but the majority of them are very likely to have another seizure at some point (6). Each seizure puts the patient at increased risk of brain and possibly bodily injury. Furthermore, multiple studies have suggested that the outcome of epilepsy surgery is dependent on the time since seizure onset; the less time to epilepsy surgery, generally the better prognosis after surgery. Even for patients with disabling mesial temporal lobe epilepsy for not more than 2 years, a recent study showed that surgical therapy is better than medical therapy in terms of both seizure freedom and quality of life (7). Based on all these factors, once a patient is thought to have DRE, discussion should be initiated with the patient regarding an epilepsy center referral.

### Obstacles to Referral

Despite a consensus that epilepsy surgery should be considered for patients with DRE, a large percentage of eligible patients are not referred to an epilepsy surgery center, and few are referred in a timely manner. Even after the release of clinical guidelines from the AAN in 2003, the average time from seizure-onset to surgical evaluation has remained about 18 years (8). There is some evidence that epilepsy referrals occur less in minorities and those without private insurance (9). In addition, the number of epilepsy surgeries has not dramatically increased.

Sometimes patients are not referred for epilepsy surgery because they are not thought to be good surgical candidates. However, as discussed in a previous subsection, there is a wide range of patients with epilepsy who might benefit from surgery, not necessarily limited by suspected seizure type, frequency, or characteristics. It is usually between the patient and their referring physician whether they are willing to take the next step. This should occur with the understanding that referral for epilepsy surgery is usually still a long way away from actual surgery, as an extensive work-up must occur first. As it remains, epilepsy surgery is underutilized.

### Where to Refer

The National Association of Epilepsy Centers (NAEC) defines guidelines and standards of care for epilepsy centers. Level 3 epilepsy centers provide basic noninvasive epilepsy care, sufficient for the Phase I monitoring described in the next section. NAEC Level 4 centers offer a more complete range of epilepsy treatment options, including Phase II monitoring and epilepsy surgery.

## SURGICAL EVALUATION PROCESS

The goal of surgical intervention is to remove all epileptogenic brain tissue, thereby hopefully eliminating all seizures. The purpose of the presurgical workup is to both identify the epileptogenic region and assess the risk of removing it. Identifying the seizure origin involves multiple electrophysiological and neuroimaging methods described later and in other chapters. Assessing the risk of surgical resection involves measuring the function of relevant regions of the brain.

Ideally, the epileptogenic region is a stable, single focus, which can be removed without any deficit in the patient's function. A fluctuating lesion, by contrast, may suggest a more systemic etiology that could recur despite resection. Similarly, multiple sources of seizures, particularly if coming from both hemispheres independently, would also imply a poor surgical outcome. If a patient does not have a resectable epileptogenic region, other advanced therapies must be considered.

### Phase I Monitoring

Surgical work-up is commonly divided into phases. Phase I is noninvasive and involves electrophysiological monitoring, neuroimaging, and functional testing. Sometimes, phase I testing is conclusive and sufficient, and the patient can proceed directly to surgical resection.

The following subsections summarize some of the techniques used to noninvasively evaluate for surgery. More details of each can be found in their respective chapters in Part II of this book.

#### *Electroencephalography and Neuroimaging*

Epilepsy resection surgery workup includes prolonged inpatient vEEG monitoring in an EMU. The goal of monitoring

is to capture as many seizures as needed in order to localize their site of origin.

Multiple seizures should be recorded, because a patient may have multifocal epilepsy, which is less amendable to surgical resection. Capturing only one or two seizures may miss different seizure foci. Also, seizures that occur close to each other in time may be the result of one persistent seizure event, and thus they should not be considered independent of each other. In other words, seizures should be separated by several hours.

Ideally, for confident ictal localization, at least four to five independent seizures with the same EEG pattern should be recorded. If the EEG pattern is different, there may be more than one site of seizure onset. Similarly, if the patient describes multiple seizure types, each type should be recorded, with the hope that they all arise from only one epileptogenic region.

Sometimes insufficient ictal recordings are captured. If this is the case, ancillary data are used. Interictal discharges are often suggestive of an epileptogenic zone. For example, frequent spike-and-slow-wave discharges over right anterior temporal head regions, without discharges anywhere else, are suggestive of right temporal seizures. In addition, the semiology of seizures often reflects its origin, along with neuroimaging results, such as MRI, PET, SPECT, and functional MRI (fMRI). Of particular use, unilateral mesial temporal sclerosis when identified on MRI is particularly suggestive of a good surgical outcome.

Concordant imaging, semiology, and interictal discharges greatly increase the confidence of seizure localization when combined with ictal EEG. On the other hand, if results are not concordant, further discussion and possibly additional testing should be done before proceeding to surgery.

#### *Neuropsychological Testing*

Neuropsychological testing involves a battery of cognitive tests used to quantify psychological function associated with neuro-anatomical structures and pathways. Preoperatively, these provide two benefits with regard to epilepsy surgery evaluation. First, they can demonstrate that a particular brain region is impaired, which may suggest brain abnormality and possible seizure origin, much like imaging studies. Secondly, neuropsychological testing evaluates brain function, and thus it could possibly predict the cognitive deficits that would occur from removal of the examined brain regions. Cognitive skills testing include memory, language, executive function, and visual-spatial perception. Impaired language skills, for example, might suggest a dominant hemisphere dysfunction. Presurgical testing is important for comparison to postsurgical testing, particularly in regard to measuring outcome. Neuropsychological testing is often an all-day process, as the battery of tests can be time consuming.

#### *Wada Test*

The Wada test involves temporarily impairing one hemisphere of the brain in order to assess language and memory



dependency on that side. This is done, typically, by injection of amobarbital by a neuroradiologist into the internal carotid artery via the femoral artery, one side at a time. This essentially puts one half of the brain “to sleep.” Once this happens, the patient is usually paralyzed on the contralateral side, sometimes with a visual field deficit. A series of brief tests are performed at this time in order to assess how memory and language are affected. The effects of amobarbital usually wear off quickly, so after about 30 minutes testing on the other side can be performed. EEG is often recorded during the procedure to document effects on brain wave activity. EEG and motor strength are often used to measure effectiveness of cortical anesthesia.

If injection into the left carotid artery greatly disrupts language and memory, but sequential injection into the right carotid artery produces minimal abnormality, then the patient likely depends on the left hemisphere for language and memory. They are likely left-hemisphere dominant, and memory is poorly supported by the right hippocampus, but well supported by the left. Resection of the right may not produce any significant cognitive deficit.

Wada test is generally well tolerated. Complications may arise from application of the medication, but serious adverse effects, such as stroke, bleeding, or infection, are rare, occurring in less than 1% of patients.

### *Magnetoencephalography and Other Tests*

Unlike EEGs, which measure electrical activity on the scalp, magnetoencephalography (MEG) measures magnetic fields around the scalp. These magnetic fields are generated by electrical activity in the brain but are less distorted by structures like the skull and muscles. Therefore, magnetic fields are good at detecting electrophysiological activity deep in the brain such as in cortical sulci. MEG electrophysiological testing is often complimentary to EEG testing.

Unfortunately, MEG machines are much more unwieldy and much less available than EEGs. They are large machines in specially isolated rooms. MEG, unlike EEG, MRI, and neuropsychological testing, is not considered standard of care in epilepsy surgery evaluation. However, epilepsy centers may choose to use them if the additional information they provide can affect treatment.

Along with MEG, there are several new diagnostic techniques being developed for the evaluation of patients for epilepsy surgery. Some involve improved sensitivities of current tests, such as increased resolution of MRI. Others look at different modalities, such as the connectivity of white-matter tracts. Still other techniques incorporate multiple modalities to improve outcome. Given the ever-changing nature of seizure diagnosis and treatment, it may be warranted to reevaluate a patient previously thought not to be eligible for surgical treatment every few years.

## **Phase II Monitoring**

Sometimes noninvasive Phase I monitoring is not conclusive, and the patient may or may not be a good surgical candidate.

In these cases, the patient will need to undergo intracranial monitoring before a resection can be recommended. This Phase II monitoring involves placement of electrodes directly on brain tissue in the operating room (OR). This is done after a plan is discussed between the epileptologist and neurosurgeon regarding where the electrodes should be placed. This is important because intracranial electrodes cannot cover the entire brain. Therefore, seizures will only be detected where the electrodes are placed, and seizures cannot be found where no one is looking. In other words, there is a selection bias. It is the responsibility of the care team to appropriately narrow the regions of interest. Sometimes this requires multiple stages of intracranial monitoring.

### *Intracranial Electrodes*

There are two standard intracranial electrode types: subdural and depth electrodes. Subdural electrodes are thin, flat disks, usually arranged in linear strips or grids, placed on the surface of the brain under the dura. They are usually positioned on the cortex where epileptogenic activity is suspected to occur. The goal is to cover all epileptogenic cortex as well as neighboring eloquent tissue. Ideally, by the end of Phase II monitoring, the epilepsy team is able draw the boundaries of both tissue types and plans a resection to include all tissue of seizure origin, without removing important brain tissue. Common placements of subdural electrodes include the lateral surfaces of frontal, temporal, and parietal lobes, inferior surface of the temporal lobe, and sometimes the medial inter-hemispheric surface.

Electrodes may also be embedded in thin flexible wires that pierce the brain. These are referred to as depth electrodes, because they are typically used to measure EEG activity deep in the brain. A common example is a depth electrode directed toward the hippocampus, a typical source for seizures. Depth electrodes are placed using stereotactic surgery, guided by coordinates determined by MRI and X-ray. They are inserted through small burr-holes, which involves less trauma to the skull and surrounding tissue than a craniotomy, which is needed to place grid electrodes. Compared to subdural electrodes they are better tolerated by the patient, and complications are generally lower. Placement of depth electrodes bilaterally can be used to lateralize the hemisphere of seizure onset. However, compared to subdural electrodes, they usually cover less cortex and involve penetrating the brain. They are used to identify deep borders of epileptogenic cortex. Sometimes, a combination of subdural and depth electrodes is used.

### *Disadvantages of Intracranial Monitoring*

Regardless of the type of electrodes used, surgical intervention is required to implant the electrodes and thus has the associated risks of general anesthesia, bleeding, and infections. The number of electrodes placed within the skull is limited by the volume the electrodes occupy and the amount of brain exposure that is required. In general, more electrodes require more exposure and a higher risk of complications.

After electrodes are placed in the OR, the patient is monitored in an EMU, as discussed earlier. Special conditions apply to Phase II monitoring when compared to Phase I. First of all, special equipment is needed. Secondly, the monitoring team must manage general postsurgical symptoms, such as pain and nausea. They must monitor for common postsurgical complications, such as infections and atelectasis. Occasionally, patients undergoing Phase II monitoring have postsurgical nausea, leading to a lack of oral intake, thus creating a ketosis-like state. This may decrease the chance of having seizures at one of the rare times where the patient is hoping to have them.

### *Advantages of Intracranial Monitoring*

The primary advantage of intracranial monitoring is increased proximity to epileptogenic tissue, and thus increased resolution of seizure-origin localization. That resolution depends on placement of the intracranial electrodes. Intracranial monitoring allows this to be customized based on prior monitoring results. It is generally limited by anatomical consideration.

Another advantage of having electrodes adjacent to the cortex is better detection of high-frequency (> 80 Hz) oscillations. There is some evidence that removal of all regions demonstrating these higher frequencies, which may be beyond the usually determined epileptogenic zone, correlates with better surgical outcome. Along with some of the advanced techniques mentioned previously, these new techniques bring hope that epilepsy surgery will continue to improve. However, more work needs to be done to prove a correlation between better technology and better outcome.

## **SURGICAL RESECTION**

Once it is determined that a patient is a good surgical candidate, the treating health care team, including epileptologist and neurosurgeon, should discuss the options available with the patient. This includes a review of all prior work-up and their implications, resection plan, expected outcomes, and possible complications. The patient should demonstrate understanding of the plan and its possible consequences. If Phase 2 monitoring is required, this discussion should take place before intracranial electrodes are removed because often resection occurs in conjunction with removal of electrodes.

Once a plan for surgery is in place and the patient is informed and comfortable with it, surgery should be scheduled as soon as the patient is ready. In some institutions, cortical mapping may occur in the operating room before resection, in order to confirm that important eloquent brain tissue is spared. However, if adequate preoperative testing was done, resection is performed without additional mapping.

### **Complications**

Epilepsy surgery puts patients at risk of the typical neurosurgical complications, including stroke, hemorrhage, and

infections. However, the most common concerns about removing brain tissue are the associated cognitive deficits. Obviously, the presurgical evaluations discussed earlier provide some guidance on potential risks. Even so, despite Wada testing, neuropsychological testing, and language mapping, up to 40% of patients, after dominant lobe resections, experience some difficulty with language (10). Thus, dominant anterior temporal resections are usually more conservative, with the posterior margin of resection not being as far back as nondominant anterior temporal lobe resections.

Another functional deficit that may arise from temporal lobe resections is a superior quadrant visual field defect. Although this defect occurs in about half of such cases, the extent of this deficit is variable and often does not affect daily functions. Other less common complications include nerve palsies and hemiparesis. Fatality is extremely rare.

Despite the associated risks of an epilepsy surgery resection, the positive outcomes of surgery generally compensate for its potential complications, such that overall quality of life improves afterward.

### **Positive Outcomes**

The commonly used Engel epilepsy surgery outcome scale divides outcomes into four categories. Classes I and II mean seizure free and rare disabling seizures, respectively. These are the best outcomes. Class III indicates worthwhile improvement, while class IV suggests no worthwhile improvement. Another system for classifying seizure outcomes after surgery was devised at Duke University. The Duke system grades patients from Class 1 to Class 3. Class 1 includes patients who are seizure free or have only auras. Class 2 patients have 10 or fewer seizures per year, and Class 3 patients have more than 10 seizures per year. The Engel system is used more often.

There has been one completed randomized control trial and multiple other studies showing that the percentage of patients seizure free, ie, Engel class I, after temporal lobe surgery is about two in three (3). The success of epilepsy surgery often persists for the long term. Most patients, about 75%, who are seizure free after 2 years remain seizure-free after 15 years, and this holds especially true for patients who are seizure free for 5 years (11). While about half of patients who have undergone an anterior temporal lobectomy are seizure free, an additional 30% achieve intermittent seizure control. Only 20% never achieve any measure of seizure control.

While the majority of epilepsy surgeries are standard temporal lobectomies and most outcome studies are based upon these surgeries, extratemporal epilepsy is often also successfully treated with neocortical resection. While patients undergoing a temporal lobectomy have about a 67% chance of seizure-free outcome, patients undergoing extratemporal surgery enjoy a less than 50% chance of seizure freedom.

As important as seizure control is on a patient's well-being, their quality of life after surgery should also be considered. This is helped by the combination of AED reduction,

or even elimination, with reduced seizures and their effects. These effects include improved independence, driving capability, employment opportunity, and overall social and lifestyle options. There is evidence that even mental health status can improve after surgery. Furthermore, the mortality risk after surgery is generally lowered and the vast majority of patients who undergo surgery say that they would repeat the process (12).

### Characteristics of Success/Failure

As discussed earlier, success with regard to seizure control depends in part on the location of the epileptogenic zone. Temporal lobe resections are more successful than frontal lobe resections. This partially correlates with the difficulty of completely defining the extent of some epileptogenic zones, as better identification ensures resection of all epileptogenic tissue. Temporal lobe epilepsy surgeries are often successful because the epileptogenic zone is often isolated to medial temporal structures.

Preoperative factors that influence surgical outcome were discussed previously. In general, a better baseline with regard to both seizure control and cognitive and mental health, along with an identified MRI abnormality, predict better postoperative quality of life.

Postoperative evaluations also may help predict surgery success. Not surprisingly, a lack of deficits and seizures postoperatively predicts better long-term outcome. More specifically, recurrent seizures in the first month to year after surgery predict worse long-term outcome (11). There is some debate whether postoperative EEGs showing interictal epileptiform discharges also portend a worse result.

## POSTSURGICAL CARE

### Withdrawal of AED

Epilepsy surgery is supposed to improve seizure control. However, particularly for the more severe cases, expectations of a cure should be tempered. The hope is to at least reduce seizure burden and also possibly reduce treatment burden by using less AEDs. If there are no seizures, then there is even the possibility of totally eliminating all AEDs.

Immediately after a resection, there is the risk of seizures due to the brain inflammation and trauma associated with surgery. AED are usually continued for at least 1 year after surgery. If a patient is seizure free during that period, then AEDs may be decreased and eventually withdrawn permanently. Ideally, epilepsy surgery reduces seizure risk enough that AED are no longer needed, but that is certainly not always achieved. There are risks to withdrawing AEDs completely, and these must be discussed with the patient.

While there is a correlation between how early AED are reduced and the likelihood of seizure recurrence, there is no clear evidence that early AED reduction predicts long-term

seizure freedom in temporal lobe resections (13). In other words, reducing AED treatment earlier only reveals persistent postoperative epilepsy earlier, but it does not seem to influence long-term prognosis. This is probably particularly true in cases where seizure freedom is more likely, but is less true when the probability of seizure freedom is less. However, if medication withdrawal is being considered, there may be evidence that doing this early is not harmful.

### Repeat Surgery

Sometimes surgery fails because a patient's epilepsy is actually not amendable to surgery, despite the presurgical estimation of success. Even so, sometimes, the potential benefits and hope of success justified the attempt. This should always be made in conjunction with the patient's full understanding and agreement.

However, occasionally, surgery fails because of technical limitations. For example, there may be complications that arise during surgery. The neurosurgeon may determine that a more extensive resection is not worth the risk. Resections may be incomplete because diagnostic testing suggests that a wider margin would cause functional impairments. In these cases, the patient may be a repeat surgery candidate. As medical technology improves, if any patient continues to have seizures, they should continue to follow-up or revisit an epilepsy center at least every few years.

When a patient with partial seizures has tried two appropriate and tolerated AEDs and still has seizures that interfere with quality of life in any way, they should be referred for consideration of epilepsy surgery (14). The goal of an epilepsy surgery work-up is to identify a single source of all seizures and confirm that its resection would not dramatically affect function. Focal abnormalities on MRI and EEG, along with better baseline seizure control and general health, are positive predictors of epilepsy surgery success. Work-up for epilepsy surgery include Phase I noninvasive EMU monitoring, MRI, and neuropsychological testing, along with possible PET, SPECT, and Wada testing. In some cases, Phase II invasive intracranial EEG monitoring is required.

For most candidates who are surgical resection candidates, the benefits of surgery greatly outweigh its risks, in terms of both seizure control and quality of life. In general, early surgery is better than postponed surgery. The most common epilepsy surgical resections done are temporal lobe resections. Ideally, AEDs can be decreased and eventually stopped 1 to 2 years postoperatively, although this should not necessarily be expected.

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# Seizure Semiology

*Dinesh V. Raju and Mohamad A. Mikati*

Seizure semiology describes the subjective and objective signs and symptoms of a seizure. These signs are used to classify seizures (Table 16.1) and provide localizing and lateralizing information about the source of the seizures. The clinical manifestations of a seizure are thought to originate from a symptomatogenic zone. A goal of seizure semiology is to identify the area of cortical tissue from where the electrical discharge of the seizures begins. However, the symptomatogenic zone does not consistently overlap with the epileptogenic zone, the area of ictal onset (1). For example, the subjective rising abdominal feeling of medial temporal lobe epilepsy is thought to originate from the insula, but the electrical origin of the seizure can be found in the medial temporal lobe. The insula is the symptomatogenic zone, and the medial temporal lobe is the epileptogenic zone. Although the symptomatogenic and epileptogenic zones may be completely or nearly overlapping, they may be some distance apart. Also, various epileptogenic zones may activate the same symptomatogenic zone, creating similar clinical seizures. The same epileptogenic zone may activate various symptomatogenic zones, generating several different types of clinical seizures (1–3).

Beyond classification, seizure semiology is an essential part of presurgical evaluation (1). It serves as a hypothesis regarding which side or specific region of the brain occupies the epileptogenic zone. Using a multimodal approach with video EEG, invasive EEG recording, imaging, neuropsychology testing, language localization, and direct electrical stimulation of cortical tissue, the epileptogenic zone may be identified in patients with the same subjective and objective signs of a seizure (1–4).

Although seizure semiology is a useful tool to classify seizures, there are limitations. There is significant variability in identifying features of seizures among trained observers. Because focal epilepsies may rapidly generalize and some generalized seizures have focal presentations, seizure semiology cannot always differentiate focal from generalized seizures. Not infrequently, inconsistent localizing and lateralizing signs may be seen during a single seizure (4).

This chapter provides a survey of the subjective and objective signs and symptoms of commonly encountered seizures and their lateralizing or localizing value.

## AURAS

Auras are subjective experiences or sensations that precede a seizure that can be objectively described. Auras may last from several seconds to minutes before or may occur with variable frequency, independent of clinical seizures. Auras are thought to be generated by abnormal epileptiform discharges that spread or evolve into an epileptic seizure. In certain cases, auras provide localizing information (Table 16.2).

## Somatosensory Auras

Somatosensory auras are often feelings of numbness or tingling that occur in the face, arm, or leg. In some cases, these sensations can “march” from the face to the arm and to the leg, as the epileptiform discharge ascends the homunculus of the primary sensory cortex, within the postcentral gyrus. The symptomatogenic zone of somatosensory auras on one side of the face or limb is the contralateral somatosensory cortex. Auras that are experienced bilaterally, in the distal extremities or trunk, can originate from epileptiform discharges within the supplementary motor cortex. Individuals with auras originating from the supplementary motor cortex may describe sequential muscle stiffness or tightening (2,5). Direct electrical stimulation of the S2 somatosensory cortex, within the superior bank of the Sylvian fissure and the posterior insula, can cause uncomfortable sensation of heat or pain (2,5–7). Thus, somatosensory auras originate from primary somatosensory area, supplementary sensorimotor area (mesial frontal), or from the secondary sensory area (superior bank of the Sylvian fissure). Diffuse warm sensations and vague general body sensations are usually of frontal lobe origin while ictal pain is usually localized to the contralateral parietal lobe.

**TABLE 16.1 Seizure Classification Based on Semiology**

Auras
Somatosensory
Visual
Olfactory
Gustatory
Autonomic
Abdominal
Psychic
Autonomic Seizures
Dialectic Seizures
Simple Motor Seizures
Myoclonic
Epileptic spasms
Clonic
Tonic
Ton–Clonic
Versive
Complex Motor Seizures
Hypermotor
Automotor
Gelastic
Special Seizures
Atonic
Akinetic
Negative myoclonus
Hypomotor
Aphasic

### Visual Auras

Simple hallucinations of bright, colorful lights, graying of vision, and dark blotches may herald an epileptic seizure or occur after the seizure. The symptomatogenic zone of these auras is often the contralateral striate cortex (Brodmann areas 17 and 18). These hallucinations are often seen in both

visual fields but can occupy a hemifield or specific quadrant, providing further localizing information. More complex visual auras with shapes and movement may originate from association cortex within the parietal and temporal lobes (2,5–8). Visual illusions are usually localized close to geniculostriate radiation and visual cortex and visual illusion of spatial interpretation to the nondominant temporal lobe.

### Auditory Auras

Auditory auras can be hearing a ringing or buzzing sound. At times, there may be a nondescript noise. The symptomatogenic zone of auditory auras is Heschl's gyrus, within the superior temporal lobe. More complex auditory auras with hearing tunes or voices are thought to originate from the temporal auditory association cortex (2,5,6,8).

### Olfactory Auras

Olfactory aura is usually a nondescript smell. The symptomatogenic zones of these auras can be the amygdala or the gyrus rectus (orbitofrontal region). These auras may be a part of medial temporal lobe epilepsy (2,5).

### Gustatory Auras

Gustatory auras are unpleasant, difficult to describe tastes. The symptomatogenic zones of these auras can be the insula or superior Sylvian bank. These auras may be a part of temporal or frontal lobe epilepsies (2,5).

### Abdominal Auras

Abdominal auras are thought to originate from insula or superior bank of the Sylvian fissure. Abdominal auras can be various gastrointestinal complaints, such as nausea;

**TABLE 16.2 Localization and Lateralization of Auras**

TYPE OF AURA	LOCALIZATION	LATERALIZATION
Unilateral Somatosensory	Somatosensory cortex	Contralateral
Bilateral somatosensory	Supplementary motor cortex	
Static visual hallucinations	Striate cortex	Contralateral
Complex visual hallucinations	Extrastriate cortex	
Simple auditory	Heschl's gyrus	
Complex auditory	Temporal association cortex	
Olfactory	Amygdala, gyrus rectus	
Gustatory	Insula	
Abdominal	Centromedian nucleus of the thalamus, basal ganglia, supplementary motor area, insula	
Autonomic	Insula, anterior cingulate gyrus	
Psychic	Temporal association cortex	



churning or twisting of the stomach; abdominal pressure with sense of needing to pass gas; and heartburn. A common feature of this aura is a sense that the abnormal feeling rises from the abdomen into the neck or face. When the aura ascends, individuals may lose consciousness. The symptomatogenic zone of these auras includes the centro-median nucleus of the thalamus, basal ganglia, supplementary motor area, and insula. Abdominal auras can be a part of temporal or frontal lobe epilepsies (2,5).

### Autonomic Auras

Autonomic auras can present as sweating, palpitation, yawning, and changes in breathing. During autonomic seizures, heart rate and respiratory rate may be measured and show abnormal rates or patterns. Unlike seizures, autonomic auras are subjective sensations that are not measured. The symptomatogenic zone of these auras can be the insula basal frontal and anterior cingulate gyrus (2,5,8). Ictal piloerection is usually ipsilateral to the seizure focus.

### Psychic Auras

Psychic auras are a misperception of the self or the outside world. Examples of psychic auras include fear, anxiety, extreme joy, déjà vu, jamais vu, and autoscopy. Déjà vu is a sense that a particular situation or experience occurred before, whereas jamais vu is a sense that the situation or experience is foreign. Autoscopy is a distortion of one's self. Individuals feel an "out of body" experience and describe a feeling of being disconnected from but being able to observe their body from a distance. In some cases, individuals are unable to perceive his/her body. The symptomatogenic zone is often temporal association cortex and limbic cortex. These auras can occur in temporal lobe epilepsies (2,5,8).

## SIMPLE MOTOR SEIZURES

Simple motor seizures are characterized by unnatural movements of one limb or the whole body in one plane (Table 16.3). These seizures can be further classified based

on the muscle groups involved, and duration and rhythm of movement. Often, electrical stimulation of the primary motor cortex or supplementary motor cortex can produce simple motor seizures (2,6,8).

### Myoclonic Seizures

Myoclonic seizures are characterized as sudden, usually nonrhythmic, jerks lasting usually less than 400 ms per jerk. These "lightening"-like jerks may occur in one limb or be generalized. Electrical stimulation of the primary motor cortex or premotor cortex can create these seizures. Myoclonic seizures occur in generalized seizures (2,6,8).

### Clonic Seizures

Clonic seizures involve semi-rhythmic to rhythmic contraction of muscles, alternating with periods of reduced muscle tone or contraction. These seizures may begin with a tonic contraction of the muscle(s) and then become clonic. Clonic seizure may be focal, involving distal extremities, such as the hand or foot. Focal clonic seizures of the face may present as pulling of one side of the faces. These seizure may spread or "march" from the distal extremity to more proximal regions, including the face (2,6,8).

Clonic seizures may be unilateral or generalized. The primary motor cortex and premotor cortex can generate these seizures. Electrical stimulation of the supplementary motor cortex can create clonic seizures of distal extremities. Frontal lobe epilepsies may include clonic seizures. In temporal lobe epilepsies, clonic seizures often involve the frontal eye fields, face, and hands, more so than the legs. In secondarily generalized seizures, clonic contractions contralateral to the seizure onset may reduce or stop before contraction ipsilateral to the ictal focus (2,5,6,8).

### Tonic Seizures

Tonic seizures commonly exhibit as persistent muscle contraction of the proximal extremities. Although both sides of the body may be involved, there is usually an asymmetry,

**TABLE 16.3 Localization and Lateralization Simple Motor Seizures**

TYPE OF SEIZURE	LOCALIZATION	LATERALIZATION
Myoclonic	Primary motor cortex, premotor cortex	
Tonic	Primary motor cortex, premotor cortex, supplementary motor cortex	Contralateral to ipsilateral seizure
Clonic	Primary motor cortex, premotor cortex, supplementary motor cortex	
Tonic-Clonic	Primary motor cortex, supplementary cortex	
Versive	Frontal eye fields	Contralateral
Epileptic spasms	Rarely, parieto-occipital region	

causing an unnatural posture or positioning of the body. These muscle contractions usually last more than 3 seconds per contraction. The appearance of the seizure can vary, depending on the symptomatogenic zone (2,6,8).

Unilateral tonic seizure usually involves one limb with significant proximal and axial involvement; these unilateral seizures are generated from the contralateral primary motor cortex or supplementary motor cortex (5,6).

When consciousness is unaffected in bilateral seizures, the supplementary motor area can be the symptomatogenic zone. When all limbs are involved, the arms at the shoulders and legs at the hips are abducted. The elbows are flexed and knees are extended (5,6).

When part of a generalized seizure, tonic seizures may begin with a crying or a moaning sound. The shoulders and arms elevate, with some elbow flexion. The body extends and takes on an opisthotonic posture with the arms flexed over the chest or extended by the sides. The hands may show wrist flexion with finger extension or wrist extension with finger flexion (2,5,6).

When a part of secondarily generalized seizures, tonic seizures can begin with contraction of the face and versions contralateral to the seizure onset. The individual may take on a “fencing posture” with the arm contralateral to the seizure onset abducted and elevated (2,6). Extension of an elbow in tonic posturing indicates a contralateral focus in 90% of the cases.

In Lennax-Gastaut syndrome, the thalamus and brainstem reticular activating system can be involved in generating focal tonic seizures. Tonic seizures are commonly seen in frontal lobe epilepsy and can be bilateral in up to one-third of cases (6). These seizures are rare in temporal lobe epilepsy, and when they do occur, they are usually unilateral (2,6).

### Tonic–Clonic Seizures

Also known as grand mal seizures, tonic–clonic seizures usually have a stereotypical progression. Initially, all limbs are extended and adducted. Individuals may appear to be a rigid board, with legs straight and arms by the side. The finger and wrists may be flexed, and the feet may be plantar flexed. The tonic phase of the seizure may last 10 to 12 seconds. The clonic phase of the seizure can involve sudden (myoclonic) flexion jerks of the knees, hips, shoulder, and/or elbows. As the seizure progresses, the frequency of the clonic phase decreases but the amplitude of the flexion jerks increases. These seizures can last up to 2 minutes in duration. Tonic–clonic seizures may be a part of generalized epilepsy or a focal epilepsy that can generalize. As with tonic and clonic seizures, the primary motor cortex and supplementary cortex are thought to generate tonic–clonic seizures (2,5,6,8).

### Versive Seizures

Versive seizure appears as turning of the eyes and head to one side. At times, there may be nystagmus, with the

fast phase directed toward the side of the initial eye turning. There may be neck extension, as well. The epileptogenic zone of these seizures is the frontal eye fields that are contralateral to the side of the head turning. There is significant lateralizing value to versive seizures, especially when they occur prior to the onset of generalized tonic–clonic seizures. Versive seizures may be a part of frontal or temporal lobe seizures (2,6,8). Nonforced head turning within 30 seconds of seizure onset is usually ipsilateral, while forced head-version (<10 s) before secondary generalization is contralateral in 90% of the cases. Version after secondary generalization is usually ipsilateral. Ictal neologistic (invention of a new word) speech occurs in dominant temporal lobe epilepsy and preserved consciousness during automotor seizures in temporal lobe epilepsy (TLE) in epilepsy from the nondominant temporal lobe.

### Epileptic Spasms

Epileptic spasms are present as symmetric tonic and myoclonic movements, involving flexion of the neck, flexion of legs at the hips, and abduction of the arms, lasting for 2 to 10 seconds. In some cases, individuals may develop an opisthotonic posture when there are axial extension movements, instead of the usual flexion movements. These seizures commonly present in infants, age 3 to 12 months. Epileptic spasms usually do not have localizing value because they are thought to originate from multiple epileptogenic zones (2,6). There are some cases of parieto-occipital seizures presenting with epileptic spasms (6,8).

### COMPLEX MOTOR SEIZURES

Complex motor seizures are characterized by automatisms, which are purposeless and unusual movements involving more than one limb and more than one plane (Table 16.4). This group of seizures may be further categorized by the type of automatisms.

### Hypermotor Seizures

Hypermotor seizures involve large-amplitude movements of the proximal muscles, usually lasting for less

**TABLE 16.4 Localization and Lateralization Complex Motor Seizures**

SIGN	LOCALIZATION
Hypermotor	Orbitofrontal lobe, supplementary sensorimotor area
Automotor	Temporal lobe, orbitofrontal lobe, anterior cingulate gyrus
Gelastic	Hypothalamus (hamartomas)

than one minute (2,5,6). Examples of hypermotor seizure are movements mimicking running or bicycle peddling, rhythmic pelvic thrusting, and rhythmic rubbing of the genitalia. Because consciousness is preserved and because of the unusual and often violent appearance of movements, these seizures may be mistaken for nonepileptic seizures (5,6). The epileptogenic zone of hypermotor seizures is thought to arise from the medial or orbitofrontal lobe and supplementary sensorimotor area (5,6,8).

### Automotor Seizures

Automotor seizures are characterized by rhythmic or semi-rhythmic oro-buccal or hand movements. Examples include chewing, lip smacking, and fumbling movements of the hands. Often these seizures are preceded by a period of motor arrest with a blank stare. Consciousness is impaired throughout these seizures. Automotor seizures with preserved consciousness are rare and associated with nondominant medial temporal lobe epilepsy. Although the epileptogenic zone is unknown in most cases, automotor seizures are a part of seizure arising from the temporal lobe or involving the orbitofrontal lobe. The anterior cingulate gyrus is thought to be involved in automatisms of the hands. When unilateral, the symptomatogenic zone is thought to be ipsilateral to the limb involved (2,5,6,8).

### Gelastic Seizures

Gelastic seizures present as laughing spells. About one-half of these seizures occur in the setting of hypothalamic hamartomas. They are also associated with seizures involving the anterior cingulate gyrus, frontal lobe, temporal lobe, and parietal lobe (2,5,6,8). Gelastic seizures sometimes occur as a sensation of pleasant feelings or pressure to laugh. Dacrystic seizure (ictal cry) occurs in patient with temporal lobe epilepsy and in those with hypothalamic hamartoma.

## DIALEPTIC SEIZURES

Dialeptic seizures are characterized by (a) significant impairment of consciousness, (b) limited or no ability to interact with the environment, (c) minimal to no movement, and (d) no memory of the event. There may be rapid eyelid fluttering and automatisms of the mouth or hands. Brief 5 to 20 second long periods of dialeptic seizures can occur with generalized epilepsies. Absence seizure is a commonly encountered example of this seizure class. Frontal lobe seizures may also involve prolonged staring spells, often longer in duration compared to those in generalized epilepsies. Staring spells followed by automatisms can occur in temporal lobe epilepsies. Although the cause of dialeptic seizures is unknown, diffuse cortical inactivation, thalamus, and upper brainstem are thought to play a role (5,6,8,9).

## SPECIAL SEIZURES

These seizures cannot be characterized as auras, motor, or dialeptic seizures but have unique features that involve a paucity of movement or alteration in cognition (Table 16.5).

### Atonic and Akinetic Seizures

Atonic seizures involve a sudden loss of axial muscle tone, leading to head drop or falls with loss of consciousness. Patients may have a brief myoclonic seizure before the atonic seizure. These seizures can be seen in individuals with generalized tonic-clonic seizures. Although the pathogenesis of atonic seizures is unclear, activation of brainstem inhibitory regions, such as the nucleus reticularis gigantocellularis or the frontal lobe negative motor areas, are thought to be involved (8).

Akinetic seizures also involve a loss of muscle tone or an inability to perform a voluntary movement, involving part of or the whole body and are thought to involve the negative motor areas of the frontal lobe. Unlike atonic seizures, akinetic seizures have preserved consciousness (6,8).

Both of these seizure types can be challenging to identify clinically. For example, cardiogenic syncope can appear similar to atonic seizures. Also postictal Todd's paralysis, complicated migraine, and transient ischemic attacks may present with altered consciousness with focal or proximal atonia.

### Astatic Seizures

Astatic seizures are falls caused by tonic, atonic, or myoclonic seizures. Sudden changes in tone or absence of tone can cause falls. The sudden jerks of myoclonic seizures can lead to imbalance, and the brief period of atonia after the jerk can lead to the fall (5,6).

### Negative Myoclonic Seizures

Similar to the phenomenon of asterixis, negative myoclonic seizures are defined by brief periods (less than 400 ms) of

TABLE 16.5 Special Seizures

TYPE OF SEIZURE	LOCALIZATION	LATERALIZATION
Akinetic, Atonic	nucleus reticularis gigantocellularis, frontal lobe negative motor areas	
Negative myoclonic seizures	primary somatosensory cortex, premotor cortex postcentral gyrus	
Aphasic	Frontal and temporal lobes	Left



atonia. These seizures may be a part of generalized or focal epilepsies. The pathogenesis of these seizures is unknown, but the primary somatosensory cortex, premotor cortex, and the postcentral gyrus have been implicated (5,6).

### Aphasic Seizures

These seizures are characterized by expressive, receptive, conduction, or transcortical aphasia and usually involve the language areas in the left frontal and temporal lobes (5,6).

### SELECTED LATERALIZING SIGNS

Numerous lateralizing movements have been described that provide lateralizing and localizing information (Table 16.6).

### Dystonic Posturing

Dystonic posturing is unnatural co-contraction of antagonistic muscles within a limb. The arm can be internally rotated at the shoulder, extended at the elbow, pronated, and flexed at the wrist. The leg may be internally or externally rotated at the hip, extended at the knee and plantarflexed. Dystonic posturing often last more than 10 seconds (1,2,5,6,8). In temporal lobe epilepsy, dystonic posturing can localize to the contralateral hemisphere and is thought to involve activation of the basal ganglia (2,5,6,8).

### Ictal Speech and Postictal Aphasia

Ictal speech is clear vocalization during a seizure, after loss of consciousness. In some cases of temporal lobe epilepsies,

**TABLE 16.6 Signs and Symptoms With Lateralizing and/or Localizing Value**

SIGN OR SYMPTOM	LOCALIZATION	LATERALIZATION
Dystonic posturing	Temporal lobe, basal ganglia	Contralateral hemisphere
Ictal speech	Temporal lobe	Nondominant hemisphere
Postictal aphasia	Temporal > Frontal lobe	Dominant hemisphere
Todd's paralysis	Motor cortex	Contralateral
Nose wipe	Temporal lobe	Ipsilateral
Unilateral eye blinking	Temporal lobe, temporo-occipital junction	Contralateral
Diffuse warmth	Frontal lobe	
Micropsia	Temporal association cortex	
Pallinopsia	Temporal lobe, temporo-occipital junction, occipito-parietal junction.	
Chills	Temporal lobe	Dominant
Rising abdominal feeling	Temporal lobe	
Uncomfortable throat feeling	Medial temporal lobe	
Ictal pleasure	Mesiobasal temporal lobe	
"Sign of 4": Extended elbow with tonic posture		Contralateral
Ictal unilateral dystonia	Temporal lobe	Contralateral
Head turning <10s before secondary generalization		Contralateral
Head turning after secondary generalization		Ipsilateral
Preserved consciousness during head turning	Frontal lobe	Contralateral
Upper extremity automatisms	Temporal lobe	Ipsilateral
Kissing	Temporal lobe	Right
Ictal cry	Temporal lobe	
Ictal speech	Temporal lobe	Nondominant
Ictal spitting	Temporal lobe	
Lateral tongue biting		Ipsilateral

this sign can lateralize to the nondominant hemisphere. Ictal speech may be confused for pure vocalization, which does not have localizing or lateralizing value (2,6,8). Postictal aphasia is an inability to generate speech, although the individual is able to follow commands and understand speech. Postictal aphasia is thought to involve the dominant hemisphere in temporal lobe epilepsies. Postictal aphasia is less common in frontal lobe epilepsies (2,5,6,8).

### Todd's Paralysis

Todd's paralysis describes unilateral limb weakness that may last up to 24 hours after the completion of the seizure. The contralateral motor cortex is thought to be involved (1,2,8).

### Nose Wipe

After the seizure, the patient indulges in hand or finger wiping or rubbing of the nose. Postictal nose wipe involves the ipsilateral hemisphere in temporal lobe epilepsies (1,2,8).

### Unilateral Eye Blinking

The sign of a single eye blinking lateralizes to the ipsilateral hemisphere (1,2).

### Ictal Nystagmus

During the seizure, there is conjugate, horizontal nystagmus. The direction of the fast phase is contralateral to the seizure focus. These seizures can arise from the occipital lobe or at the temporo-occipital lobe junction (2,8).

Semiology of seizures can be very helpful in not only trying to establish the putative site of onset of seizures but also whether a seizure is epileptic or otherwise. Symptoms before, during, and after the seizure can help in this localization. Accurate localization can be helpful in guiding further investigations and treatment. Seizure semiology factors are prominent when patients are being evaluated for surgical treatment of their epilepsy. It should be remembered, though, that the symptomatic zone of the seizure might not always consistently overlap with the epileptic zone.

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# Scalp Video EEG Monitoring

*Abeer J. Hani and Aatif M. Husain*

While about 60% to 70% of patients with epilepsy will respond to a first- or second-line antiepileptic drug (AED), the remaining 30% to 40% end up developing medically resistant epilepsy. In these refractory cases, epilepsy surgery when possible is often considered to give these patients a chance at seizure freedom. The presurgical workup often involves careful analysis of the clinical semiology and electrographic presentations of the patient's seizures in order to identify the ictal onset zone. To achieve that, scalp video EEG (vEEG) monitoring is used as a first fundamental step. Scalp vEEG is used to identify spells that mimic seizures and to identify patients with nonepileptic seizures (NES), particularly psychogenic NES (PNES).

In this chapter, an overview of the preparations needed to start scalp vEEG monitoring including AED withdrawal is presented. Following that, the common interictal and ictal patterns seen in the setting of presurgical evaluation using scalp vEEG monitoring will be highlighted. Finally, the range of EEG findings seen in PNES will be reviewed.

## PREPARATIONS FOR vEEG MONITORING

### Technical and Personnel Considerations

vEEG monitoring is often performed in specialized units referred to as epilepsy-monitoring units (EMU). The National Association of Epilepsy Centers (NAEC) has published detailed guidelines on the technical aspects of EMU monitoring (1).

Given the relative ease of use and the synchronized acquisition of video and EEG recordings, digital vEEG acquisition systems are now widely used in various epilepsy centers.

The presence of experienced personnel including EEG technologists and nurses is very important to provide continuous surveillance of the patient and the recording. Many centers also have 24-hour technologist assistants who watch the vEEG recordings and immediately notify the clinical staff of any seizures to allow for timely interventions. This,

however, does not obviate the need for an observer, often a caregiver, present in the patient's room who can identify events and press the EEG event button when an event occurs.

The review of the vEEG by experienced neurophysiologists and epileptologists must always be available even after hours, which often involves remote access to the vEEG study. Dedicated information technology (IT) personnel often can help set up such access and monitor the appropriate recording of large volumes of data.

### Patient Safety

It is well known that patients with epilepsy may sustain multiple types of seizure-related injuries, including head, dental and soft tissue injuries, as well as fractures. The more serious of these injuries includes tongue bites, vertebral compression fractures, shoulder dislocations, subdural hematomas, and skull fractures seen with falls. There is also risk for sudden unexpected death in epilepsy patients (SUDEP) and prolonged seizures/status epilepticus (SE), mostly in patients with poorly controlled seizures and generalized tonic-clonic (GTC) seizures. Besides these potential risks, postictal psychosis has been found to arise rarely in the setting of vEEG monitoring and is seen more often in patients with medically refractory temporal lobe epilepsy (TLE) (2).

When vEEG monitoring is conducted for presurgical evaluation or spell characterization, the patient's seizures are often induced using various provocative measures like photic stimulation, hyperventilation, sleep deprivation, visual patterns, video games, mental calculation, and most seriously rapid AED withdrawal (3). Ensuring the patient's safety is important in the EMU when spells are being induced. There is no one single way of ensuring complete safety, but padding the bed rails should be performed routinely and maintaining constant 24-hour surveillance may help lessen the likelihood of potential complications.

Standardized plans and protocols to address SE, postictal psychosis, and falls also help ensure the readiness of



the clinical team and avoid undue delays and confusion in periods of acute seizure emergencies.

### Antiepileptic Drug Withdrawal

The limited time available to record an adequate number of seizures for presurgical evaluation often prompts the rapid tapering of the patient's home AED regimen. There has been no consensus on how to best wean AEDs. Most of the literature available is based on expert opinions and surveys (4). The recurring theme is the need to individualize the rate and degree of AED withdrawal to patient- and drug-related factors. It is vital to know the frequency of seizures prior to admission and the presence of previously seen seizure-related complications, as well as the risk for seizure clustering and SE. In case of previous admissions for presurgical evaluation, inquiring and obtaining records that detail need for AED withdrawal and rate of seizure occurrence during these admissions may be very helpful. A patient with high seizure frequency may not require medication withdrawal, whereas patients with high risk for seizure clustering may merit a cautious, slow taper. The consensus is that slow withdrawal is overall favored over fast withdrawal and that close monitoring as medications are being withdrawn is very important. One approach is taper one medication by 33% to 50% on the first monitoring day and then to continue reducing the doses of other AED at a similar rate on each subsequent day until a sufficient number of seizures has been recorded (5). The plan of tapering AED should be clearly discussed with the patient, caregiver, nurses, and medical team.

## USE OF vEEG FOR SEIZURE LOCALIZATION

### Clinical Localization

The use of vEEG monitoring as part of the presurgical evaluation for epilepsy surgery permits the observation of the clinical semiology of the seizure and the detection of localizing signs by reviewing the video of the event. These signs often aid in determining the site of seizure onset and progression. A detailed discussion of localizing signs and seizure semiology may be found in Chapter 16.

### Electrographic Localization

The EEG is analyzed to identify interictal and ictal abnormalities that further aid in localizing the ictal onset zone. Often electrodes are placed according to the International 10-20 system of electrode placement. Other electrodes including subtemporal chains or more specific electrodes according to the 10-10 system may be used to further help in seizure localization. Optimal EEG analysis often requires the use of bipolar and referential montages.

### Interictal Abnormalities

Interictal abnormalities include intermittent or continuous focal slowing and suppression as well as focal or generalized

epileptiform abnormalities. The location, type, frequency, and association with specific awake, asleep, or rapid eye movement (REM) states need to be identified for these abnormalities. In cases of multifocal discharges, the burden of discharges present in each region may need to be evaluated by performing a spike count. This is especially important in cases of bitemporal epilepsy and has been found in some studies to be predictive of the degree of seizure freedom following resection. A sample of these interictal abnormalities can be found in Figures 17.1–17.4.

### Ictal Patterns

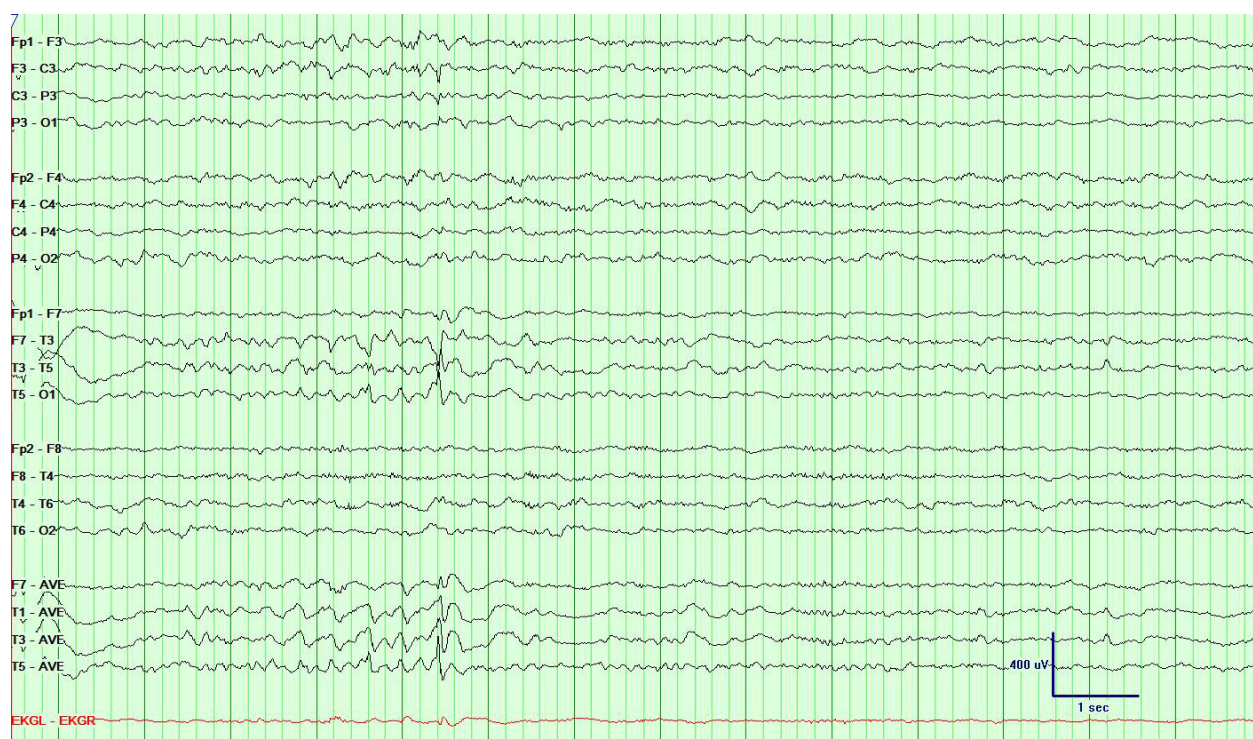
The most important factor in the presurgical evaluation for epilepsy surgery is the careful analysis of the EEG ictal pattern. In this discussion, only the ictal patterns of partial seizures will be discussed, as most generalized seizures are not considered for surgical treatment. Often, such patterns have a definite onset, evolution, and end. The onset could be non-specific with either focal or generalized desynchronization, low-voltage fast activity, or irregular focal or bilateral delta activity (6).

It is important to know that scalp vEEG monitoring has several limitations. To start with, simple partial seizures have an EEG correlate in only 20% to 30% of the cases. This is in contradistinction to scalp changes seen in about 85% to 90% of complex partial seizures. Frontal lobe seizures, however, may not show a clear ictal pattern on scalp EEG. This is thought to be due to the large surface area of the mesial and inferior frontal cortex that is hard to assay using scalp EEG monitoring. A retrospective study of 72 patients with Engel Class I surgical outcomes showed that ictal EEG localization was possible in 57% of all seizures and in 72% of all patients. False localization occurred in 6% of the seizures, occurring in 28% of occipital seizures and in 16% of the parietal seizures (7). Excessive myogenic artifacts that obscure the recording at times may preclude adequate localization of seizure onset.

The ictal EEG patterns vary depending on the brain regions where seizures start and will be discussed in the following sections.

*Mesial temporal lobe epilepsy.* The most common ictal onset pattern seen in patients with mesial TLE is lateralized rhythmic theta or alpha pattern and may be seen 10 to 40 seconds after clinical seizure onset (Figure 17.5). This pattern is seen in about 80% of patients with mesial TLE and, when present, it correctly lateralizes seizure onset in 95% of patients. The presence of ipsilateral postictal focal slow EEG activity further confirms the suspected ictal onset zone.

*Neocortical temporal lobe epilepsy.* Neocortical TLE often has broader distribution of interictal discharges and ictal rhythmic activity. The ictal onset is often slower, broader, and less focal than that of mesial TLE (Figure 17.6). The evolution of the seizures is also less stable in both frequency and amplitude and higher-voltage activity may be seen in the parasagittal electrodes.

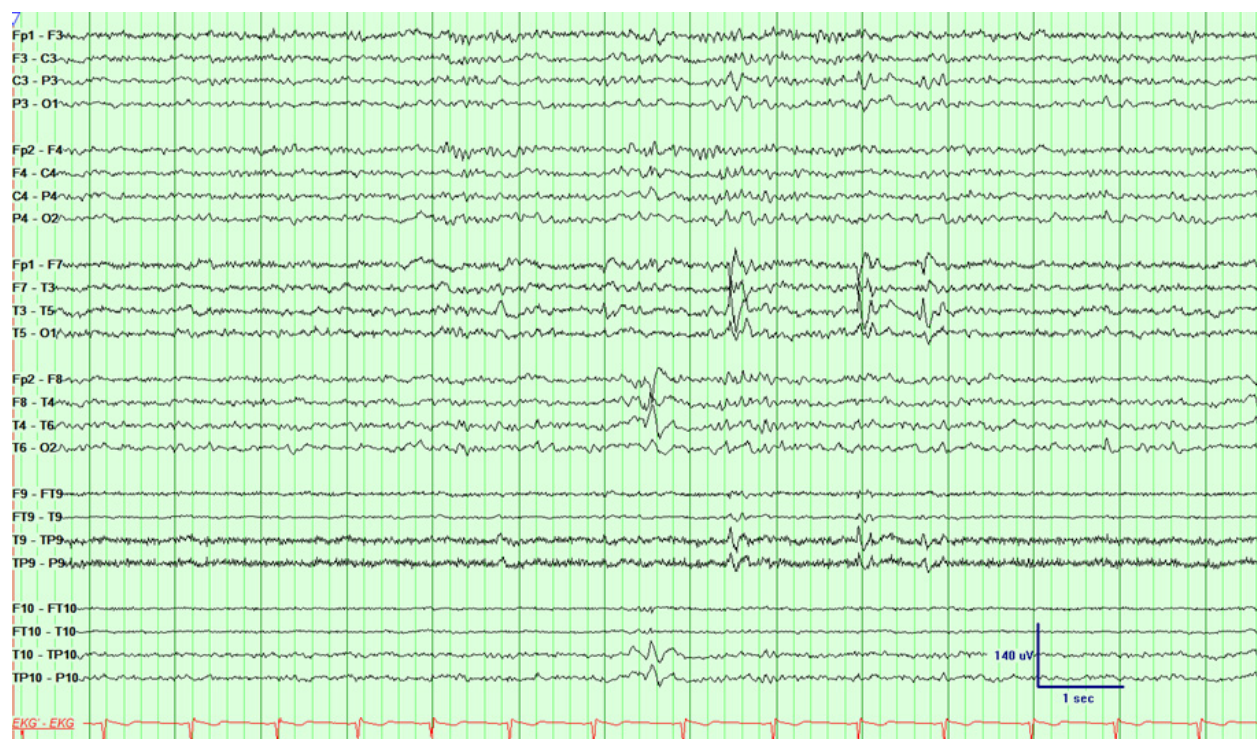


**FIGURE 17.1** Interictal abnormalities in a patient with left temporal epilepsy in the form of left temporal spikes and intermittent left temporal slowing. Note that the bottom 4 channels belong to a referential montage and show that the spike is of highest amplitude at T5.

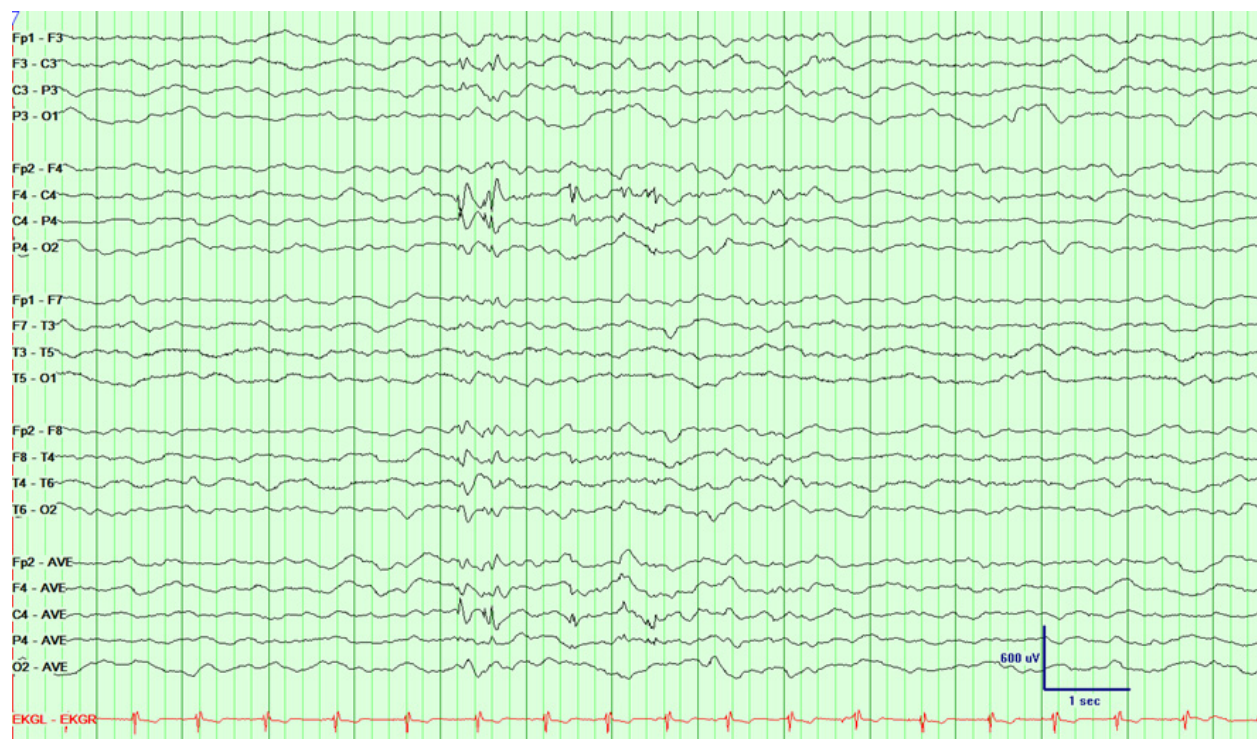


**FIGURE 17.2** Interictal EEG showing left temporal intermittent rhythmic delta activity (TIRDA) seen in a patient with suspected left temporal lobe epilepsy with evidence of left mesial temporal sclerosis.





**FIGURE 17.3** Interictal EEG showing independent bitemporal spikes and sharp waves in a patient with suspected left temporal epilepsy in the setting of left mesial temporal sclerosis. Spike count done showed 75% predominance of the spikes and sharp waves in the left temporal lobe and 25% in the right temporal lobe.



**FIGURE 17.4** Interictal EEG showing right central spikes in a patient with suspected extratemporal epilepsy, later found to be right lateral frontal epilepsy using invasive recording. The bottom 4 channels display a referential montage showing that the spike is of highest amplitude at C4.



**FIGURE 17.5** EEG showing ictal onset in a patient with suspected mesial temporal lobe epilepsy. The use of the subtemporal chain aids in localization of seizure onset. Notice the left temporal fast rhythmic theta activity at seizure onset. The patient has evidence of bilateral mesial temporal lobe sclerosis on her brain imaging.

*Frontal lobe epilepsy.* Frontal lobe seizures often do not have a clear, if any, localizing ictal pattern. Ictal onset and evolution may appear generalized, often reflecting secondary bilateral synchrony. With the hypermotor mesial frontal lobe seizures, excessive movement and muscle artifacts may obscure the EEG recording. Figure 17.7 shows an example of a left lateral frontal lobe seizure that could not be clearly localized using scalp EEG requiring more invasive monitoring. Orbitofrontal seizures often propagate to the ipsilateral temporal region or frontal region and may cause erroneous localization of seizure onset zones.

*Parietal lobe epilepsy.* Parietal lobe epilepsy is considered the most difficult to evaluate and localize with scalp EEG monitoring. Less than 10% of the ictal patterns are well localized to the parietal regions and 30% of them are associated with secondary bilateral synchrony. Often invasive monitoring is needed for these types of epilepsies.

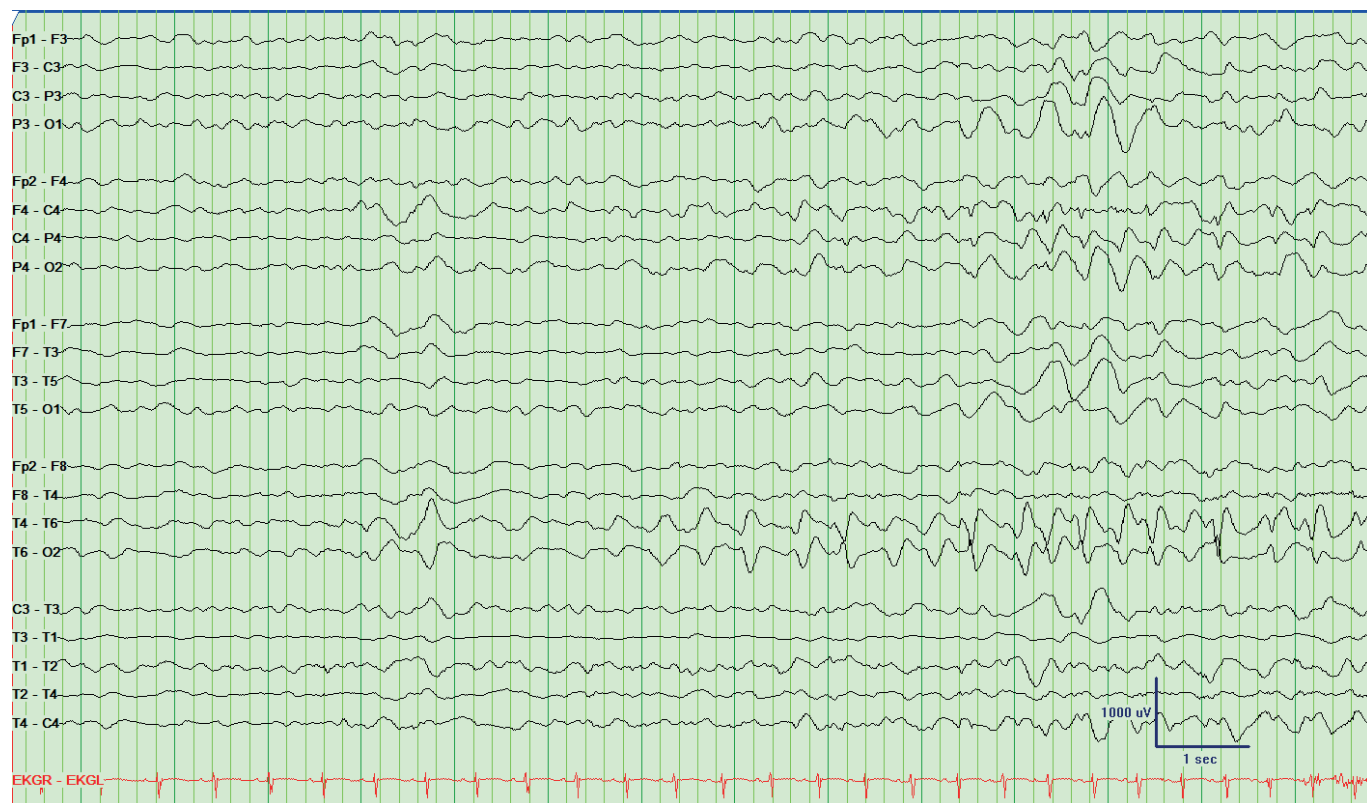
*Occipital lobe epilepsy.* The ictal patterns are poorly localizing in occipital lobe epilepsy as well. Ictal patterns localizing to the occipital region are seen in only 15% to 20 % of patients. Often there is rapid spread to the motor areas with secondary generalization or to the ipsilateral temporal lobe mimicking mesial TLE. The clinical semiology with visual symptoms is more helpful than the EEG in suggesting an occipital onset.

## USE OF vEEG FOR SPELL CHARACTERIZATION

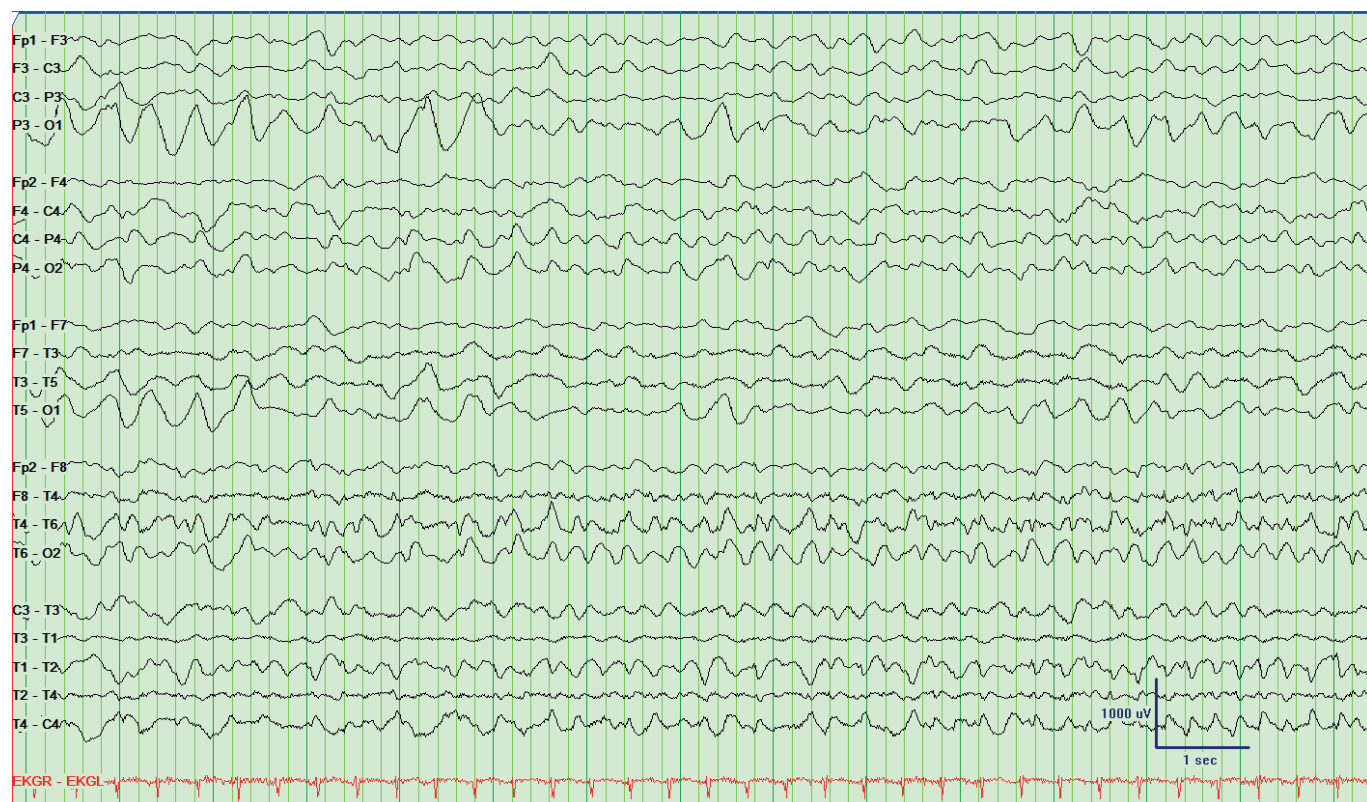
Although EEG monitoring is most widely used in the setting of presurgical evaluation for seizure localization, scalp vEEG is considered the gold standard to differentiate epileptic from nonepileptic spells. There are many seizure mimickers that are discussed in other chapters where the use of vEEG may be very helpful. However, the discussion in this section will be focused on evaluation of PNES.

It is estimated that 15% to 30% of patients referred to the EMU for refractory epilepsy have PNES. The first step in the identification of PNES is suspecting the diagnosis. This could sometimes be done through obtaining a detailed history, but the actual observation of the clinical behavior and interpretation of the EEG during an event is most helpful in establishing the diagnosis. When watching the video of such events, there is often gradual onset and termination of the event along with other clues that may suggest PNES, including pelvic thrusting, eye closure, asynchronous movements, lack of stereotypy, side-to-side arrhythmic head movements, and opisthotonic posturing. Given that simple partial seizures and some frontal lobe seizures may show no clear EEG changes, watching the video for these clues helps rule out the possibility of partial seizures without ictal patterns. Sometimes capturing multiple events helps determine the true nature of the spells. The ILAE has put together a staged approach outlining the minimum requirements to diagnose PNES. It includes elements of the history, use of EEG, and





(A)



(B)

**FIGURE 17.6** Ictal EEG showing right posterior temporal onset (A), with subsequent evolution in the frequency of the ictal activity immediately afterward (B). This patient had suspected periventricular heterotopia in her left and right temporal lobes.

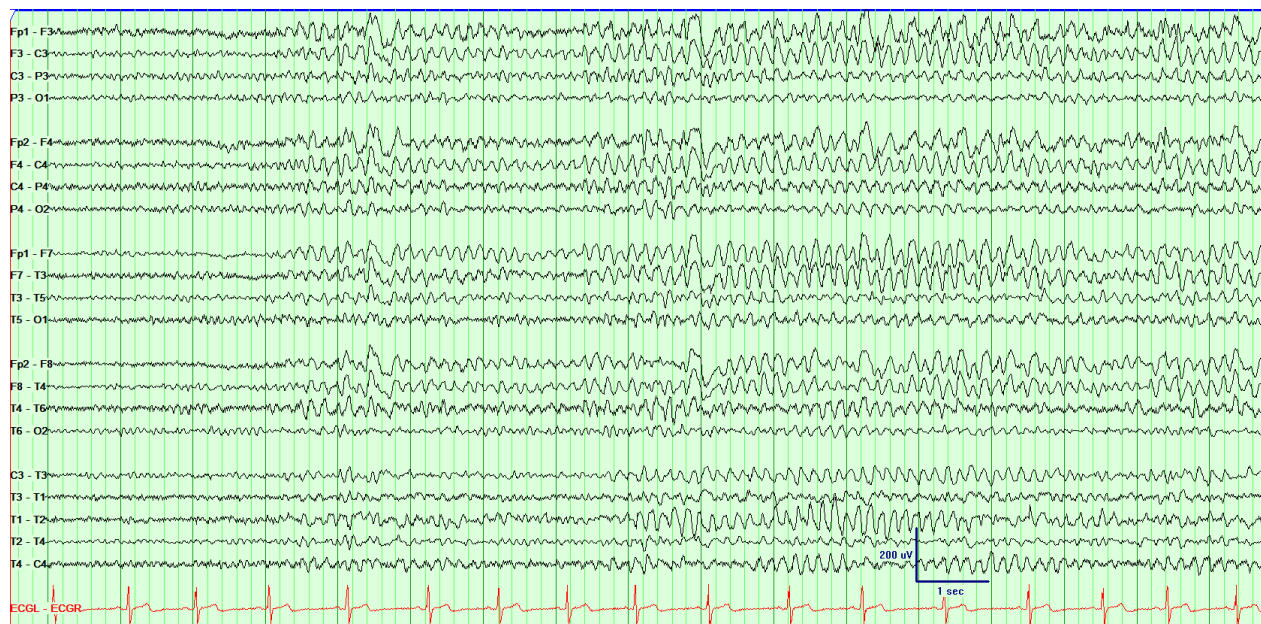


**FIGURE 17.7** Ictal EEG showing bilaterally synchronous onset with better evolution in the left hemisphere in a patient with left lateral frontal epilepsy who had undergone invasive monitoring that localized the seizure onset to the left hand area.

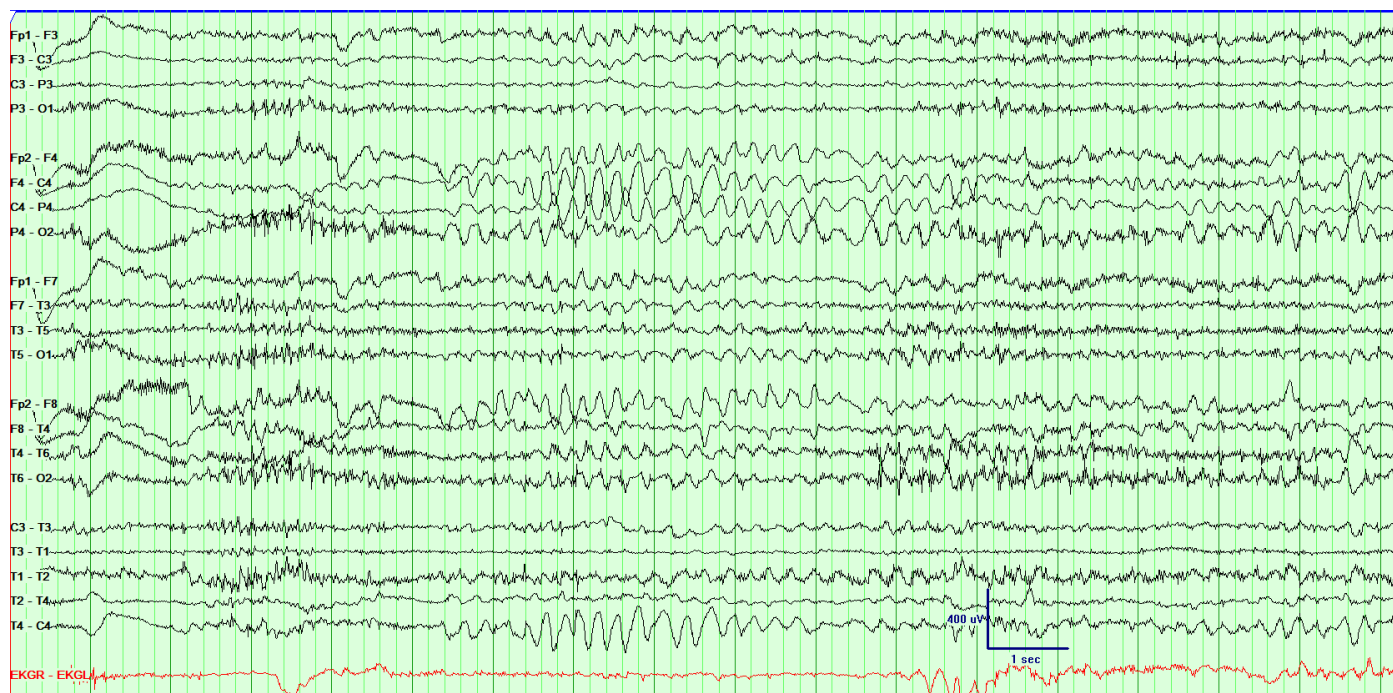
other investigations (8). The suggestibility of the events and the ease with which the events may be provoked also help identify PNES.

The EEG is often normal and shows no ictal patterns or epileptiform abnormalities during the events. In cases of excessive movement or muscle artifacts, the EEG recording may be hard to interpret. The review of EEG recordings in patients who were wrongly diagnosed with epilepsy showed over-reading of

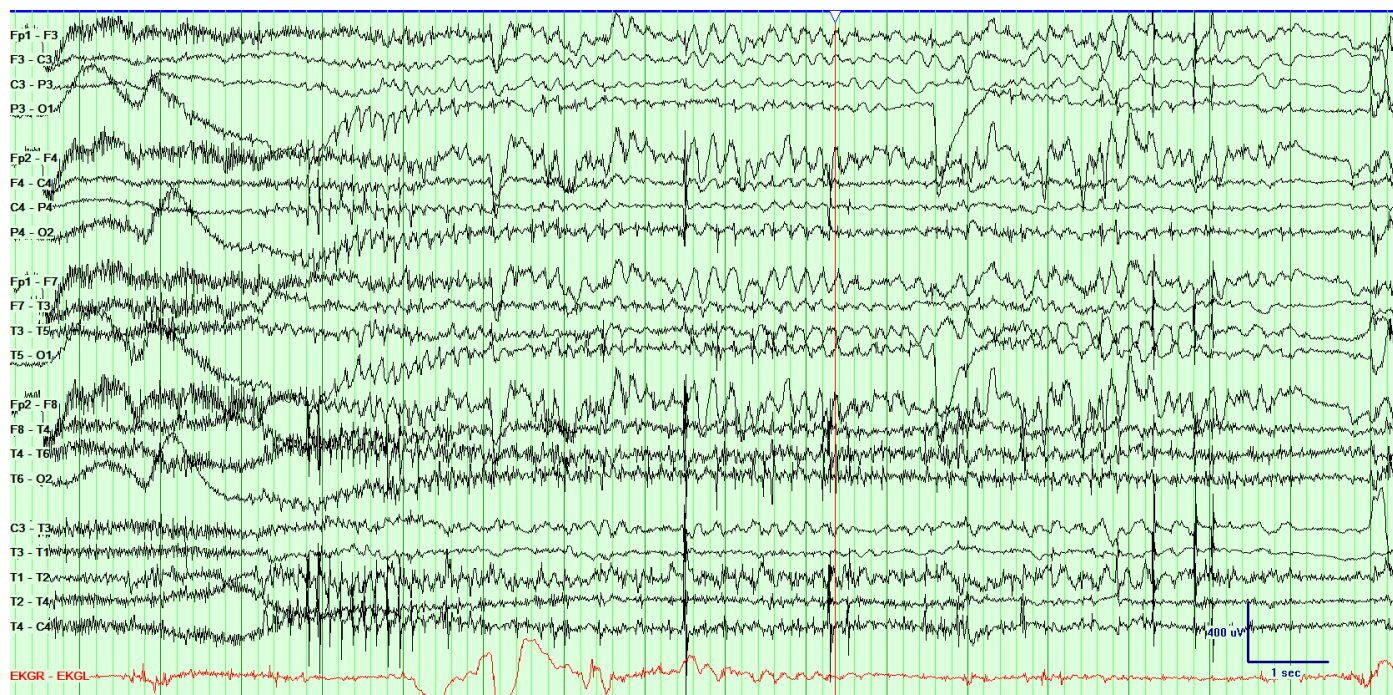
patterns that are normal variants or variations of normal background activity. A good knowledge of these common variants and common artifacts seen in EEG recordings is important to avoid misinterpretation. Figure 17.8 shows an example of midline theta of drowsiness, which is a normal variant that may be mistaken for an ictal pattern. Figures 17.9–17.12 show various examples of EEG recordings during PNES, highlighting some of the typical EEG findings seen during these events.



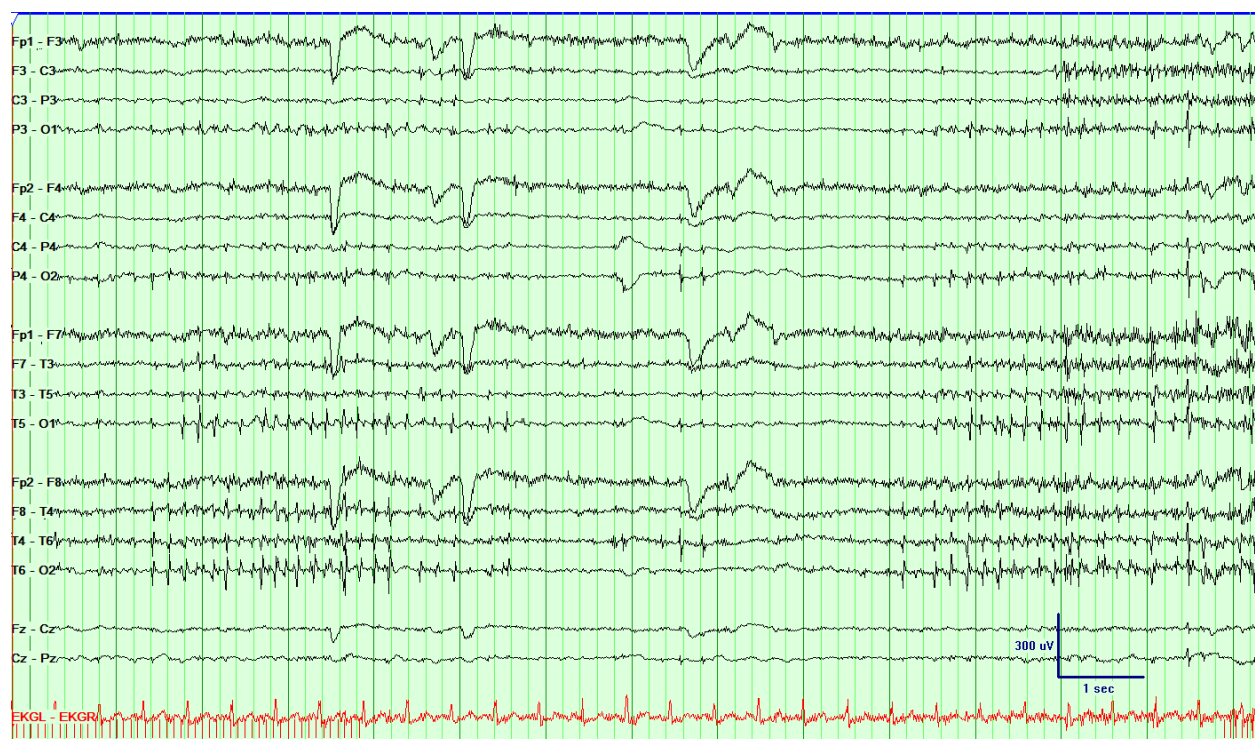
**FIGURE 17.8** EEG showing a normal variant, midline theta of drowsiness, in a 17-year-old adolescent with history of generalized tonic-clonic seizures. It is important to identify these rhythms to avoid misinterpretation of the recording. Although there is some waxing and waning of the amplitude, there is no significant change in the frequency of this normal pattern.



**FIGURE 17.9** EEG during monitoring for spell characterization. The patient started shaking with asynchronous movements that would wax and wane with eyes closed. EEG shows no clear evolution or buildup with myogenic artifact seen during the event.



**FIGURE 17.10** EEG showing another event of the same patient as that shown in Figure 17.9. Notice again the fast myogenic artifact seen with the fast whole body movement. The patient had opisthotonic posturing and eyes closed during this event with whole body trembling.



**FIGURE 17.11** EEG showing repetitive poor rhythmic myogenic artifact during a PNES induced by intermittent photic stimulation. The patient was having small amplitude front-to-back poorly synchronous head movements and would pause briefly when asked to interact with examiner.



**FIGURE 17.12** EEG recording during a PNES of staring and poor responsiveness. This recording shows persistence of the normal awake baseline background during the event.



Scalp vEEG monitoring is considered a very important first step in the presurgical evaluation of patients with refractory epilepsy with the aim of identification of the ictal onset zone. It is also the gold standard for identification of PNES. Specialists with sufficient training and expertise in epilepsy should perform detailed evaluations of the clinical manifestations as well as the EEG findings of patients admitted for vEEG monitoring. This will ensure the accurate diagnosis and localization of seizures and give patients the chance to receive the most appropriate care possible.

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# Intracranial EEG Monitoring

*Saurabh R. Sinha*

In spite of an ever-increasing number of available antiepileptic drugs (AEDs), a substantial portion of patients with epilepsy are intractable to treatment, due to either lack of efficacy or severe side effects. For patients with focal-onset seizures who are intractable to medications (continued seizures in spite of adequate doses of at least two appropriate AEDs), trial of additional medications and medication combinations offer little chance of achieving seizure freedom. In these patients, surgical resection of the seizure focus may offer the best chance for achieving seizure control. The basic requirement for resective surgery for intractable seizures is the ability to localize the “epileptogenic zone” (EZ), the region of the brain that is presumably initiating the seizures (1). More practically speaking, the EZ is the region whose resection/removal will fully control the seizures. Different aspects of the epilepsy surgery evaluation lead to identification of related areas. For example, imaging studies may identify an “epileptogenic lesion” that is the presumed etiology of the seizures; however, the EZ can be within the lesion, near the lesion, or even distant from the lesion. Interictal EEG may identify epileptiform discharges, which identify the “irritative zone”; this zone often includes the EZ but may be larger than, smaller than, or even remote from the EZ. Clinical semiology can help to define regions of the brain involved in the seizure, the “ictal symptomatogenic zone”; however, many brain regions are clinically silent or have nonspecific semiologies. Thus, the ictal semiology may just reflect areas to which the seizure spreads after starting in the EZ. The region of ictal EEG onset (“seizure onset zone”, SOZ) is thought to most closely approximate the EZ in most cases. However, even the SOZ is limited due to the inability to record EEG from the entire cortex and the potential for rapid spread of seizure activity. In some cases, when the SOZ, clinical semiology, “irritative zone,” and “epileptogenic lesion” are concordant, the EZ can be adequately identified by noninvasive means.

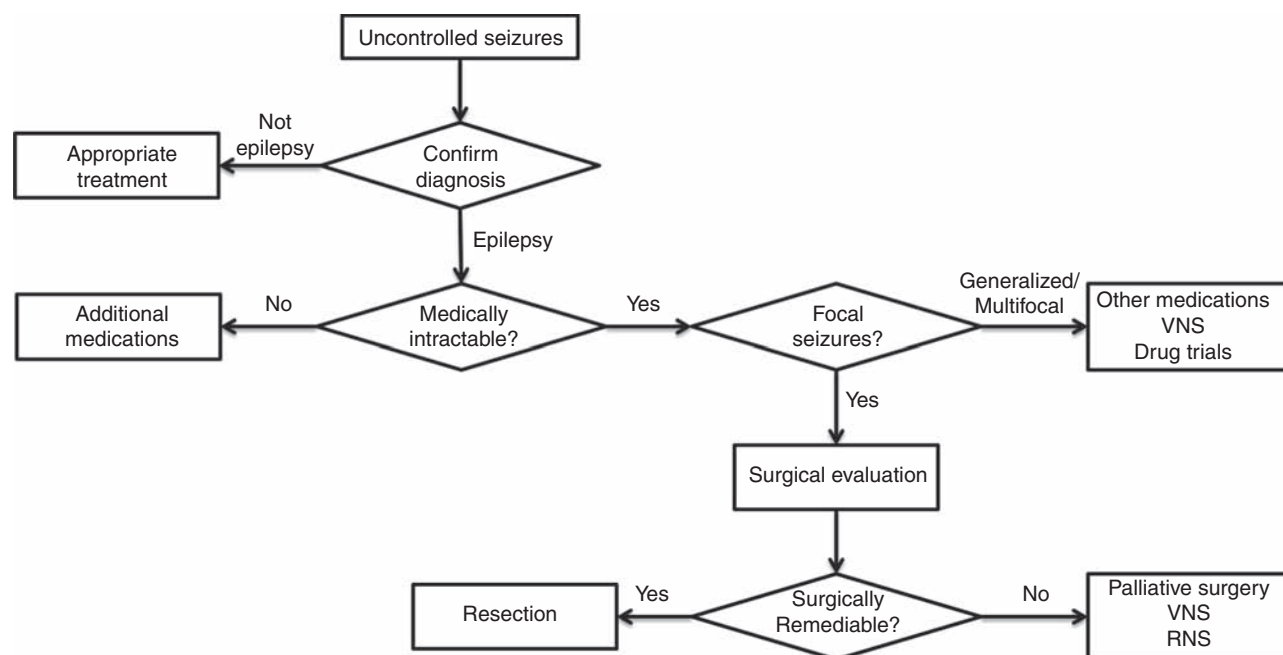
A second requirement for resective surgery is being able to assess the risk of the planned resection to eloquent

cortex, those regions whose removal would lead to significant functional deficits. This can sometimes be done or presumed based on neuropsychological testing, functional MRI, Wada testing, and the presumed typical function of certain brain regions. However, in many cases, brain mapping is necessary to truly assess the risk of resecting a brain region. When the EZ cannot be adequately localized and/or the risk to eloquent cortex cannot be adequately determined based on noninvasive testing, intracranial recordings are needed to evaluate for epilepsy surgery.

## NONINVASIVE EVALUATION FOR EPILEPSY SURGERY

The initial evaluation of a patient for potential epilepsy surgery starts with establishing that the patient has intractable epilepsy (Figure 18.1). It is important to confirm that the patient actually has epileptic seizures and that all the events in question are epileptic. A significant proportion of patients referred to epilepsy centers for evaluation end up having nonepileptic events (most commonly psychogenic nonepileptic seizures), in part or in whole. If the events in question are epileptic, it is important to establish that they are truly intractable. Too often, reported medication failures are actually related to side effects, inadequate dosing, noncompliance, or inappropriate choice of medications. The history should also provide a detailed description of the semiology of all seizure types in a given patient. This can not only provide important hints about the location of the EZ, but can also raise warnings about the potential for multiple foci. Most commonly, however, multiple seizure types described by a patient are actually variable expressions of a single seizure focus; for example, seizures with or without secondary generalization.

It is also important to review any prior evaluation the patient may have had. Routine EEGs can provide hints about areas of neuronal dysfunction (focal slowing) and epileptogenic potential (interictal epileptiform discharges)



**FIGURE 18.1** Flow chart for evaluation of patient with seizures that have not responded to treatment.

Abbreviations: RNS: responsive neurostimulator; VNS: vagus nerve stimulator

that may be part of the EZ. Although these should also occur in the video EEG (vEEG) that is an essential part of the evaluation, prior recordings may offer additional information about multiple foci. A high-quality MRI of the brain can also provide important clues about the location of the “epileptogenic lesion.” The MRI should be performed on at least a 1.5T (ideally a 3.0T) scanner with high-resolution T1-weighted images of the entire brain and, in patients with any concern for a temporal lobe focus, thin-cut T2-weighted coronal images through the temporal lobes. Personal review of the MRI is essential as subtle findings like mild cortical dysplasia, early mesial temporal sclerosis, and subtle asymmetries are often not reported in routine MRI reports.

The next step in most evaluations is a vEEG. The primary goal of the vEEG is to record the actual epileptic seizures to better characterize the EZ. It is important to capture the patient’s stereotypical seizures, including different types, if they exist. The vEEG is useful to confirm the semiology of the seizures as well as their EEG features. Patient- and family-reported seizure semiology is often inaccurate or incomplete. The EEG features will ideally lateralize and localize the seizure focus; however, this is sometimes limited due to seizures onset in regions far from the scalp (eg, mesial temporal, orbitofrontal, or midline cortical regions) or in small regions with rapid spread to other, even contralateral regions.

The need for additional testing, like PET and SPECT scans, is usually based on the results of the initial evaluation. For patients with a presumed epileptogenic lesion, if all

the data are concordant with the lesion and the lesion is far from eloquent cortex, it may be possible to proceed straight to resection (Table 18.1). However, if the data are discordant or there are other red flags (Table 18.2), intracranial recording is often needed.

### CANDIDATE SELECTION FOR INVASIVE MONITORING

As discussed earlier, only when the various pieces of data are concordant and the presumed lesion is far from eloquent cortex can one proceed straight to resection of the presumed epileptogenic lesion. In most other circumstances, including nonlesional cases (Figure 18.2), invasive monitoring is

**TABLE 18.1** Requirements for Epilepsy Surgery Without Invasive Recording

1. Well-localized ictal-EEG
2. Semiology consistent with presumed seizure focus
3. Lesion on structural or functional imaging studies consistent with seizure focus
4. Absence of other potentially epileptogenic lesions on imaging or EEG
5. Seizure focus remote from known/presumed eloquent cortex
6. Presumed etiology of epilepsy does not predispose to diffuse or multiple foci: tumor, vascular malformation, mesial temporal sclerosis

**TABLE 18.2 Red Flags From Noninvasive Epilepsy Surgery Evaluations**

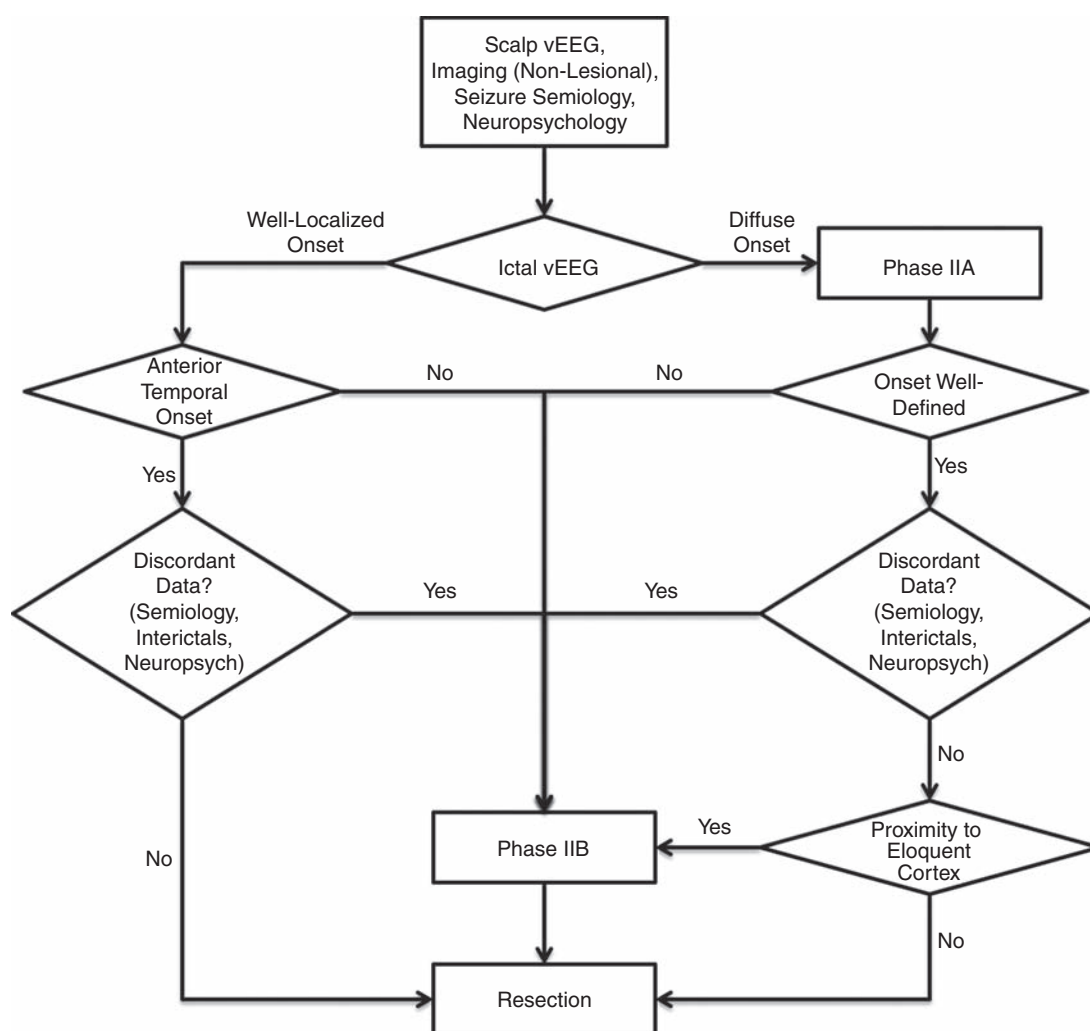
1. Discordant data: interictal EEG, ictal EEG, semiology, imaging studies
2. Nonlesional cases
3. Ictal-EEG pattern significantly delayed compared to clinical onset
4. Proximity of presumed seizure focus to eloquent cortex
5. Presumed etiology of epilepsy predisposes to diffuse or multiple foci: cortical dysplasia, h/o encephalitis, h/o trauma

needed in order to localize the EZ and resect it safely. For lesional cases (Figure 18.3), intracranial recording may still be required if the various pieces of data are not concordant, if the lesion/etiology is one commonly associated with multifocality, or if the lesion is close to eloquent cortex. If the

data still localize to a single hemisphere or a region of a single hemisphere, unilateral electrode implantation may be adequate (Phase IIB monitoring, see definition later). However, if the discordant data raises the concerns for both the hemispheres or widespread regions within a single hemisphere, a multistep surgical process may be needed: first implanting electrodes through burr holes to cover both the hemispheres or widespread regions (Phase IIA, see later) followed by Phase IIB over the region found in Phase IIA monitoring.

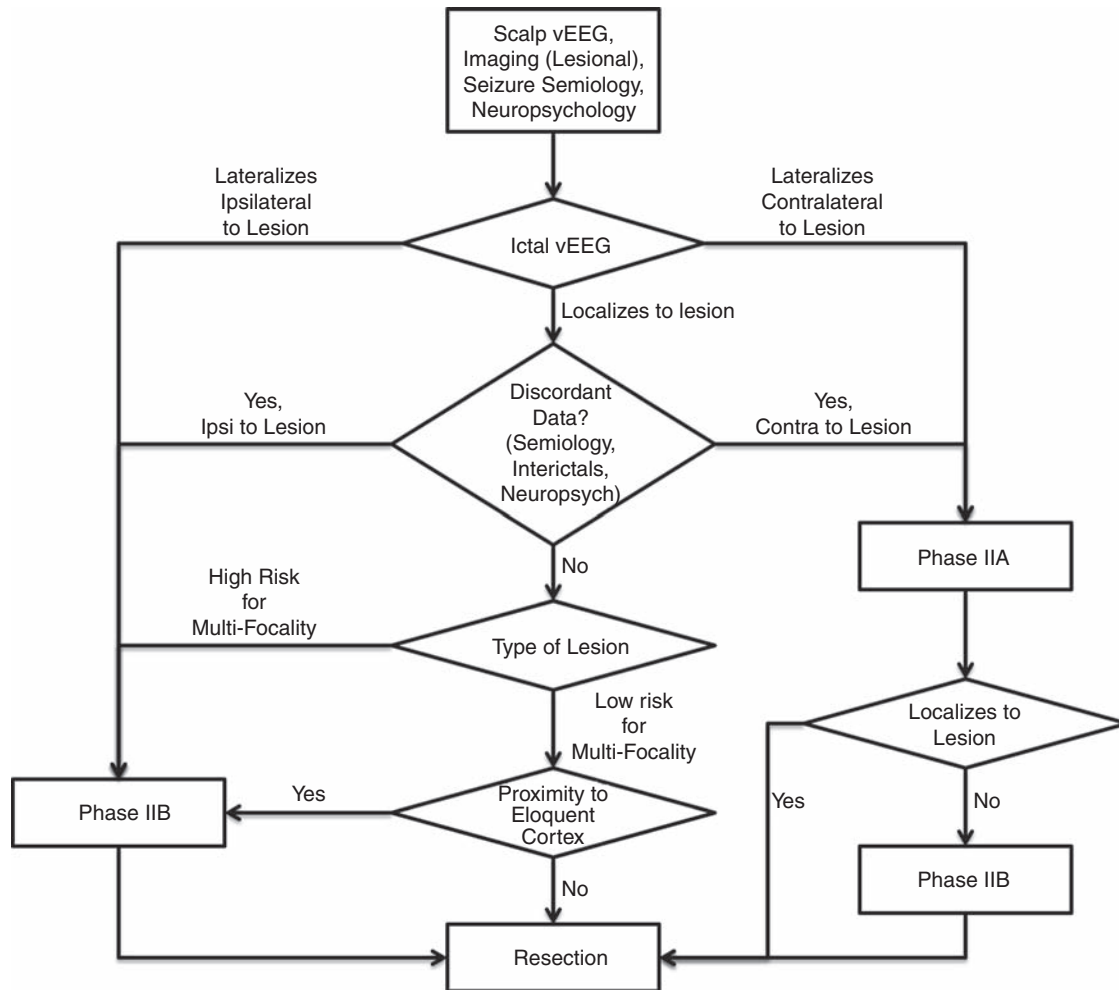
### TYPES OF INVASIVE MONITORING

Invasive monitoring can be done both acutely (in the operating room only) and “chronically” (for days to weeks using implanted electrodes). In the acute situation, electrodes are placed by the surgeon during the operation. These can be



**FIGURE 18.2** Flow chart for evaluation of patient with intractable focal-onset seizures without a potentially epileptogenic lesion on imaging.





**FIGURE 18.3** Flow chart for evaluation of a patient with intractable focal-onset seizures with potentially epileptogenic lesion on imaging.

used to identify interictal discharges and map brain function. Ictal recordings are usually not possible; however, in some circumstances, the interictal data and brain mapping results may be enough to proceed to resection. Much of early epilepsy surgery was performed using only acute recordings.

However, most invasive monitoring now involves the chronic implantation of electrodes. This is referred to as Phase II monitoring. As mentioned previously, Phase II can be further subdivided into IIA and IIB. The key distinction is that at end of Phase IIB, the intention is to have collected all the data needed to resect the epileptogenic focus at the time of electrode removal. Phase IIA usually involves a more widespread sampling of the brain using electrodes implanted over a wide region, often bilaterally. The goal of Phase IIA is usually to lateralize the epileptogenic focus and possibly roughly localize it to a specific lobe or region; at the end of monitoring, the electrodes are removed without a resection being performed. In most cases, phase IIB

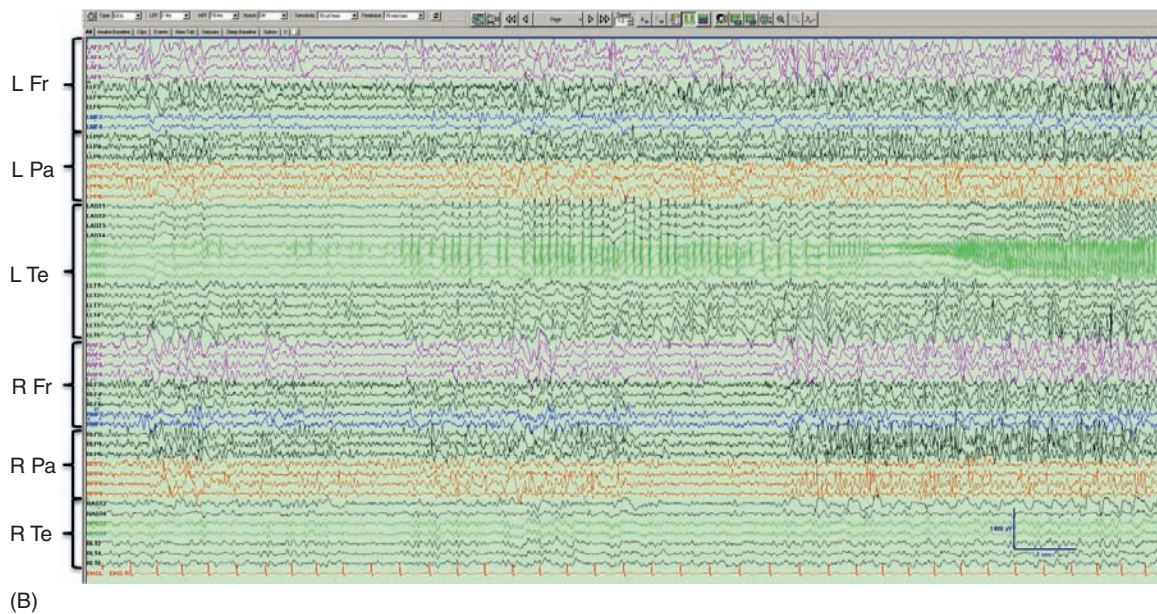
monitoring is subsequently performed prior to actual resection of the focus (see Figure 18.4). A subset of phase IIA patients may be able to proceed to resection without additional intracranial monitoring—usually those where seizures are ultimately localized to the anterior or mesial temporal lobe. Another subset may be found not to be candidates for respective surgery—for example, if phase IIA reveals clearly multifocal seizures.

### PLANNING OF INVASIVE MONITORING

Although invasive monitoring provides significant advantages for localizing the focus and mapping brain function, there are some important limitations to keep in mind. The most important is the potential for sampling error. Signals are only obtained from tissue immediately underlying/surrounding the electrode. Thus, any brain regions not covered by electrodes will not be recorded. Invasive monitoring must be approached as a hypothesis-driven exercise.



(A)



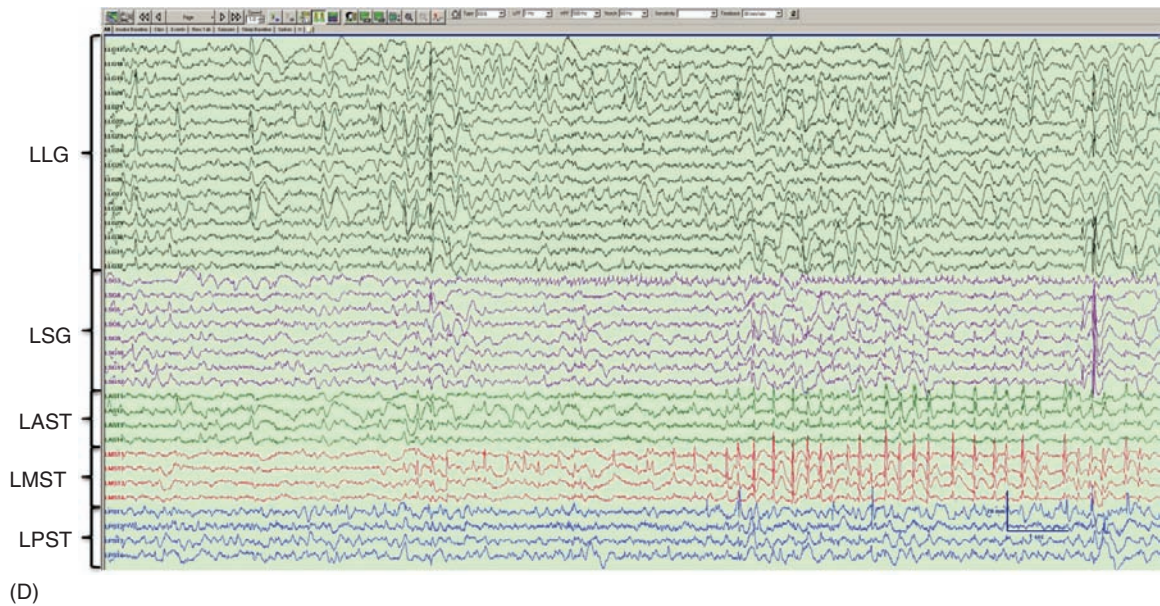
(B)



(C)

**FIGURE 18.4** ECoG of clinical seizures in an adult patient who underwent multistage evaluation for intractable seizures since childhood and nonlesional imaging. Scalp recording was nonlateralizing. (A) Lateral skull x-ray showing electrode placement for Phase IIA. Electrodes were inserted through three burr holes on both sides of the head. (B) Habitual clinical seizure showing onset in the L temporal region (LPST1-2) with spikes. Electrodes are grouped by brain region. Every other contact is shown. (C) Lateral skull x-ray showing electrode placement for Phase IIB. A  $4 \times 8$  grid (LLG) was placed over the left lateral temporal lobe. A  $2 \times 6$  grid (LSG) was placed in the subtemporal/suboccipital region. Three strips (LAST, LMST, and LPST) were placed over the subtemporal surface. (Continued)





**FIGURE 18.4** (Continued) (D) Habitual clinical seizure showing onset in the anterior portion of the subtemporal grid (LSG3) with slowing/sharp waves, followed by alpha frequency activity. The pattern spreads rapidly to nearby LMST. The patient underwent a left temporal resection (mainly inferior).

Abbreviations: Fr: frontal; L: left; Pa: parietal; R: right; Te: temporal.

**TABLE 18.3** Planning Electrode Placement

1. Areas of concern for seizure-onset zone based on:
  - a. Imaging (potential lesions)
  - b. Seizure semiology
  - c. Interictal and ictal scalp EEG recording
  - d. Areas that are clinically or electrographically silent (on scalp EEG):
    - i. Orbitofrontal region for temporal lobes
    - ii. Interhemispheric regions for frontal, parietal, or occipital lobes
    - iii. Insular cortex for temporal or frontal lobes
2. Areas of concern for eloquent cortex—allow mapping and definition of margins

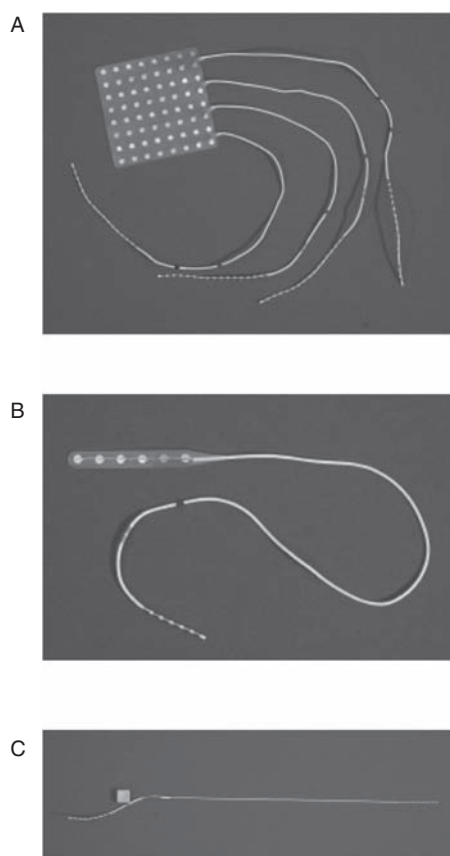
Based on the results of the noninvasive evaluation (EEG, semiology, imaging), one should identify candidate regions for the EZ. Special attention should be paid to structures that are not well recorded by scalp EEG or that produce nonspecific or subtle semiologies. Electrode coverage must be planned to allow for both identifying the EZ and ruling out other candidate areas (Table 18.3). It may also be important to cover areas to insure that eloquent cortex can be confidently identified using brain mapping. Based on these requirements, one can very quickly formulate a plan involving numerous electrodes. This has to be tempered by the higher risks for infection, herniation, patient discomfort, and other complications posed by larger numbers of electrodes (2).

## TECHNICAL ISSUES FOR INVASIVE MONITORING

### Electrodes

There are a wide variety of electrodes that are routinely used for intracranial recording. These include grids, strips, and depth electrodes. Grids and strips consist of metal discs embedded in a plastic or polymer sheet with an exposed metal surface for recording. The most common types are made from metals like platinum alloys shaped into approximately 5 mm diameter discs with approximately 3 mm diameter exposed surface. For acute recordings, stainless steel electrodes are sometimes used. The discs are commonly spaced 10 mm apart (center to center), although other spacings like 5 or 15 mm are also available. Grids are available in many sizes, ranging from 2 × 4 electrodes to 8 × 8 electrodes (Figure 18.5A). Strips, by definition, have one row of electrodes and commonly range from 1 × 2 to 1 × 10 electrodes (Figure 18.5B). A variety of configurations are available from vendors including customized ones for special applications.

Strips and grids can only be placed on the cortical surface; recording from deeper structures requires depth electrodes (Figure 18.5C). These are also available in various sizes and electrode spacings. Compared to subdural electrodes, these can take substantially longer to implant and pose a higher risk of hemorrhage. However, once implanted, they are often better tolerated, may be associated with a lower risk of infection, and can be left in for longer periods of time. Multiple, usually bilateral, depth electrodes that are placed stereotactically using imaging guidance form the



**FIGURE 18.5** Examples of intracranial electrodes. (A) An  $8 \times 8$  contact grid. (B) A  $1 \times 6$  contact strip. (C) An 8 contact depth electrode.

basis of stereo-EEG. This technique is used widely in Europe and is gaining in popularity in the United States.

### Implantation Procedure

During electrode implantation, it is absolutely crucial that the configuration (location and orientation) and identity of electrodes (usually indicated by colored bands on the electrode tails) be accurately recorded. Once the electrodes have been placed, the tails are tunneled under the skin (to reduce infection risk and provide stability). Thus, after skin closure, it is difficult to know which tail belongs to which electrode. It is also important to recognize that the final electrode placement may not exactly match the planned implantation as practical issues, like bridging veins and adhesions, may dictate electrode location (Figure 18.6).

For recording, a reference electrode is needed. This can be a selected contact of the implanted electrodes (one believed to overlie a relatively inactive area) or can be an additional electrode implanted just for this purpose (eg, a  $1 \times 4$  strip placed facing the scalp rather than the cortex). Outside the operating room, the electrode tails are then connected using special connectors to the EEG recording equipment (via a headbox). Skull x-rays, computed tomography

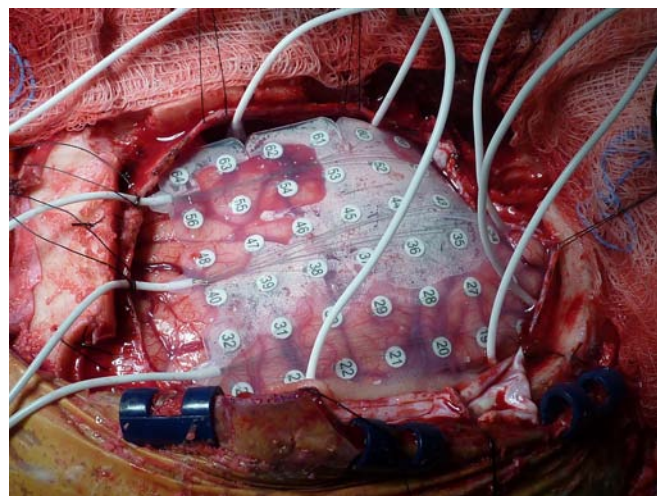
(CT) scans, or MRI are performed after electrode placement to confirm electrode locations.

### Clinical Issues During Phase II

Patients must be monitored carefully while they have implanted electrodes and immediately after removal. Antibiotics are routinely used as prophylaxis for reducing infections. In many cases, steroids are at least transiently given to reduce edema and inflammation. Patients are often admitted to a critical care unit for 12 to 24 hours after implantation to be observed closely for acute complications. Once in the epilepsy monitoring unit (EMU), they must still be monitored for both seizures and neurological deterioration related to surgery. Tapering of AEDs is often aggressive (may be initiated prior to implantation) due to importance of recording enough seizures during the planned implantation—longer implantations are associated with higher complication rates, especially infections.

### EEG Equipment/Settings

The EEG equipment used for electrocorticography (ECoG) is essentially the same as that used for scalp recording. However, typically, they are capable of recording many more channels (128 and 256 channels are common). The low-frequency filter settings are usually about 0.5 or 1.0 Hz; high-frequency filter settings are typically greater than 100 Hz. High-frequency activity is often of interest in ECoG, thus filter settings of greater than 200 or even greater than 500 Hz are sometimes used. The desired frequency range dictates the necessary sampling rate: typically greater than 400 Hz, often approaching 1 to 2 kHz. Higher rates are often used for research and potentially clinical purposes (eg, to accurately record activity like high-frequency oscillations



**FIGURE 18.6** Placement of an  $8 \times 8$  grid over the left temporal lobe. Multiple strips are also shown (only their tails can be seen).



[HFOs]). With a large number of channels and high sampling rates, it is possible to cause significant delays in displaying/reviewing data, even with relatively fast review stations.

### Removal of Electrodes and Resection

At the conclusion of intracranial monitoring, the resection is planned based on the collected data—to include the electrodes involved in seizure onset and to exclude or limit those felt to be functionally important. The electrode tails are cut at the scalp. After removal of the bone flap and opening of the dura, the desired area of resection is marked using anatomical landmarks or markers prior to removal of the electrodes. Cultures are usually sent at multiple stages during electrode removal (from different tissue layers and electrodes) to aid in identification of the responsible organisms if an infection arises in the postoperative period.

## ELECTROCORTICOGRAPHY

Epileptiform discharges are more evident on ECoG than on scalp EEG. This is a result of both improved access to deep structures and higher sensitivity. Many patients without interictal discharges on scalp EEG will have interictal discharges on ECoG. It is estimated that 6 to 10 cm<sup>2</sup> of superficial cortex have to be involved in an epileptiform discharge for it to be apparent on scalp EEG (3); however, less than 1 cm<sup>2</sup> is necessary for the activity to be apparent on ECoG. Interictal epileptiform discharges (IED) on ECoG typically have significantly greater amplitude (up to 1 mV in some cases) and are shorter in duration, sometimes less than 20 msec. Like IEDs on scalp recording, those on ECoG may appear in regions distant from the EZ.

Dysplastic cortex often produces a unique pattern of epileptiform abnormalities on ECoG. Prominent, widespread IEDs that may be very complex, repetitive, and have a polyspike morphology are typically seen. Nearly continuous spikes and periodic spikes can also occur. It has been suggested that beyond localizing dysfunctional/epileptogenic cortex, the specific morphology of IEDs may be predictive of cortical dysplasia.

There are several types of nonepileptiform abnormalities that may be observed on ECoG. For the reasons discussed earlier, normal background activity may be misinterpreted as abnormal: the activity is often of higher amplitude and contains faster frequencies than those observed on scalp EEG. Because ECoG is rarely, if ever, performed on normal brains, there is little data on the appearance of normal patterns on ECoG. Finally, local factors such as cortical geometry, the presence of blood vessels, blood, or abnormal tissue can lead to changes in the amplitude of ECoG. In most cases, it is not valid to make comparisons

about amplitudes between ECoG electrodes as many factors contribute.

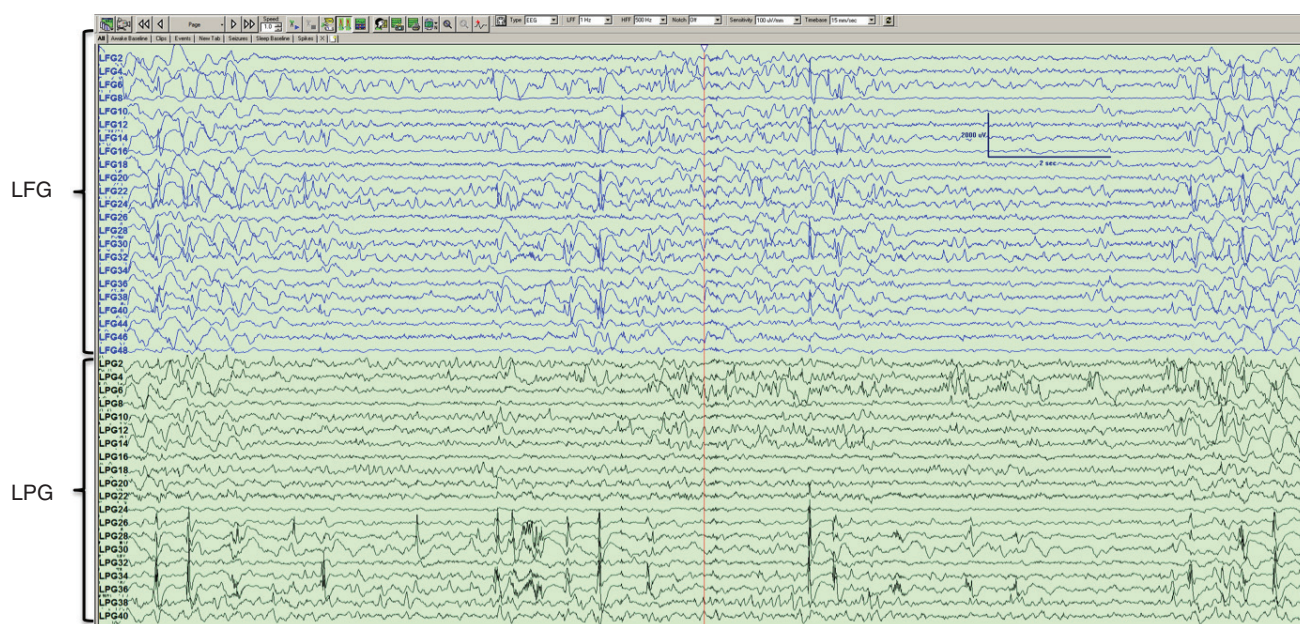
Focal slowing may be recorded on ECoG. This usually reflects dysfunctional cortex and may be helpful when IEDs are not present on the pre-excision ECoG. Like IEDs, however, the lack of specificity limits its usefulness.

Pathological alterations of brain function may be indicated by certain abnormalities. Interictal epileptiform discharges, while strongly associated with the EZ, are clearly seen in much more widespread areas, especially in intracranial recordings. Thus, there is a need for other, more accurate markers of the EZ. HFOs, including gamma frequency oscillations (30–80 or 100 Hz, often considered separately from HFOs), ripples (80 or 100–250 Hz), and fast ripples (250–500 or 600 Hz) have been recorded using intracranial electrodes. Early examples relied on microelectrodes (thin wires inserted directly into the cortex as part of a larger array of typical intracranial electrodes). Subsequently, HFOs have been demonstrated with standard macroelectrodes used for clinical ECoG and even in scalp recordings. HFOs are typically of low amplitude and brief duration (a few 100 msecs). Analysis in the past required painstaking review of short samples of ECoG (often <10 min); however, algorithms have been developed (still on a research basis) for semi-automated detection, which can now be performed faster and on larger time samples. Although these oscillations clearly occur in both epileptogenic and nonepileptogenic tissue, they are seen more commonly in the seizure-onset zone. HFOs that are associated with interictal epileptiform discharges may be especially useful as a biomarker for the seizure-onset zone. Gamma oscillations that are closely associated with an interictal epileptiform discharge may be especially selective for the seizure-onset zone (4); in fact, it has been a long-held belief of many neurophysiologists that interictal discharges associated with fast activity (Figure 18.7) are more selective for the seizures-onset zone.

In retrospective analysis, it has been demonstrated that removal of regions showing HFOs, especially fast ripples, is correlated with better seizure outcomes. However, they are clearly not purely a biomarker—their occurrence and frequency appear to be affected by many factors including spatial location and stage of sleep (5). Improvements in analytical techniques for identifying HFOs and larger studies to elucidate their characteristics and association with the EZ are needed prior to their clinical use.

## SEIZURE DETECTION

As in scalp recording, there are a variety of electrographic seizures patterns that can be seen during ECoG. These include irregular or rhythmic spike/sharp waves, low-voltage fast activity, electrodecremental activity, and sinusoidal or rhythmic discharges (6). However, the higher sensitivity of ECoG and the relative lack of artifact make these patterns easier to recognize. The ictal pattern on ECoG should start



**FIGURE 18.7** Sample of interictal ECoG from an adult patient with history of perinatal left parietal infarct and intractable seizures. Selected electrodes are shown from a  $6 \times 8$  contact grid placed over the left frontal region (every other electrode shown) and an  $8 \times 8$  grid over the left parietal region (superior 5 rows, every other electrode shown). Abnormalities shown include high-amplitude spikes (eg, LFG24, 32, 40 and LPG 26, 28, 34, 36, 38), some with associated gamma frequency activity (LPG 36), as well as focal slowing (LPG 28, 30).

before or at least simultaneously with clinical onset. If the clinical seizure starts first, it is a strong indicator that the true SOZ is not being recorded.

The higher sensitivity of ECoG also has the potential to make physiological rhythms look pathophysiological—patterns may appear ictal that are not. Meaningfully defining what constitutes an ictal pattern has not been easy. In the broadest terms, any pattern that is sustained ( $>5$ – $10$  sec) and shows evolution (change in pattern, frequency, or spatial extent) may be an ictal pattern. Association with behavioral seizures obviously increases the likelihood that the pattern is ictal.

Much more so than in scalp recording, subclinical seizures (ictal electrographic pattern without associated clinical event) are a relatively common finding in ECoG (Figure 18.8). Ideally, these are a milder or limited version of the pattern associated with clinical events. However, the situation often arises where subclinical seizures are seen from areas removed from the onset zone of the clinical/habitual seizures. In these cases, the decision to include these electrographic-only ictal-onset zone electrodes in the resection must be made on a case-by-case basis.

## BRAIN MAPPING

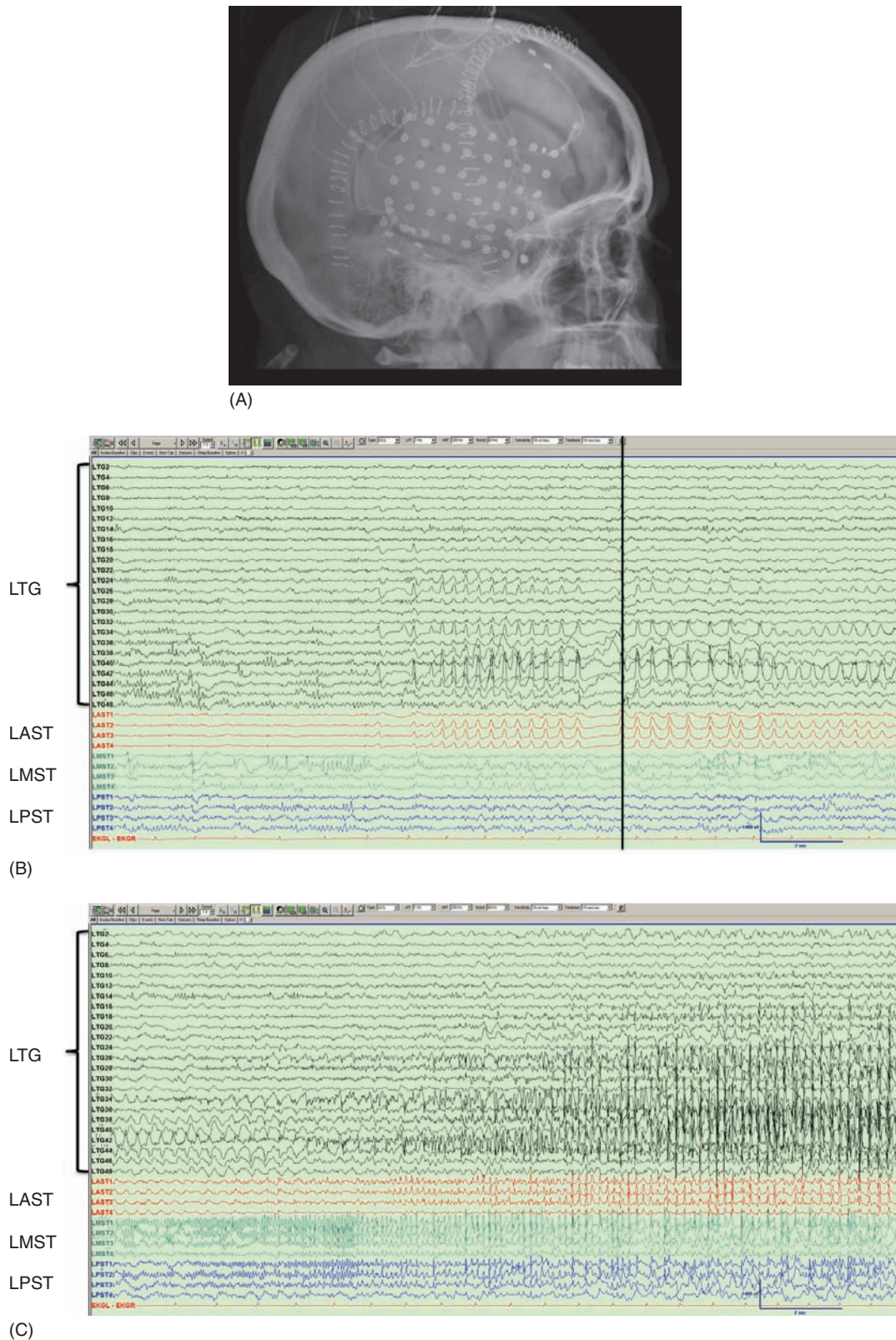
Functional brain mapping is a critical part of most intracranial EEG recordings. It is used to localize functional areas

such as primary and supplementary cortex, receptive and expressive language areas, and sensory and special sensory cortices. The proximity of these regions to the presumed SOZ is an important determinant of the extent of resection that can be performed. In an ideal situation, there is no overlap between the functionally important areas and the SOZ. When there is a significant overlap, there needs to be a discussion with the patient about acceptable risks/deficits for seizure control; the likelihood of seizure control may need to be compromised to avoid deficits (Figure 18.9).

## RISKS OF INTRACRANIAL RECORDING

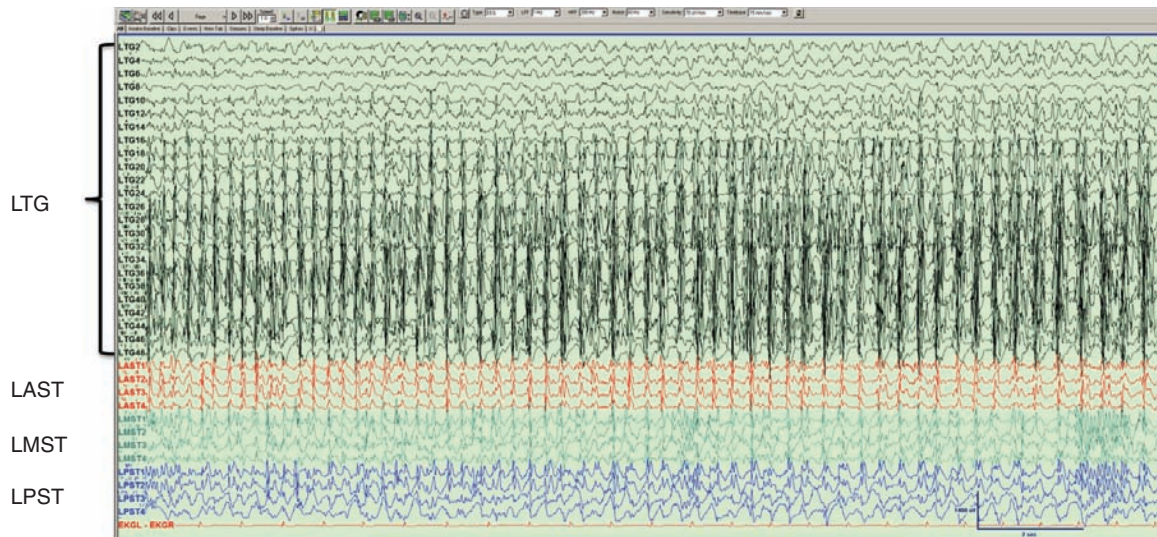
Implantation of intracranial recording poses certain additional risks above and beyond that of resection epileptogenic tissue. These include intracranial infections, superficial infections, intracranial hemorrhage, and elevated intracranial pressure (2). Factors that potentially increase risks include the number of electrodes implanted, duration of implantation, age of patient, and implantation of the dominant hemisphere. Up to 4% of patients may require additional surgical procedures for management of complication, eg, evacuation of a hematoma or treatment of intracranial infections. Depth electrodes have the potential for causing acute hemorrhagic complications, but may have an overall lower complication rate, especially for infection and increased intracranial pressure.



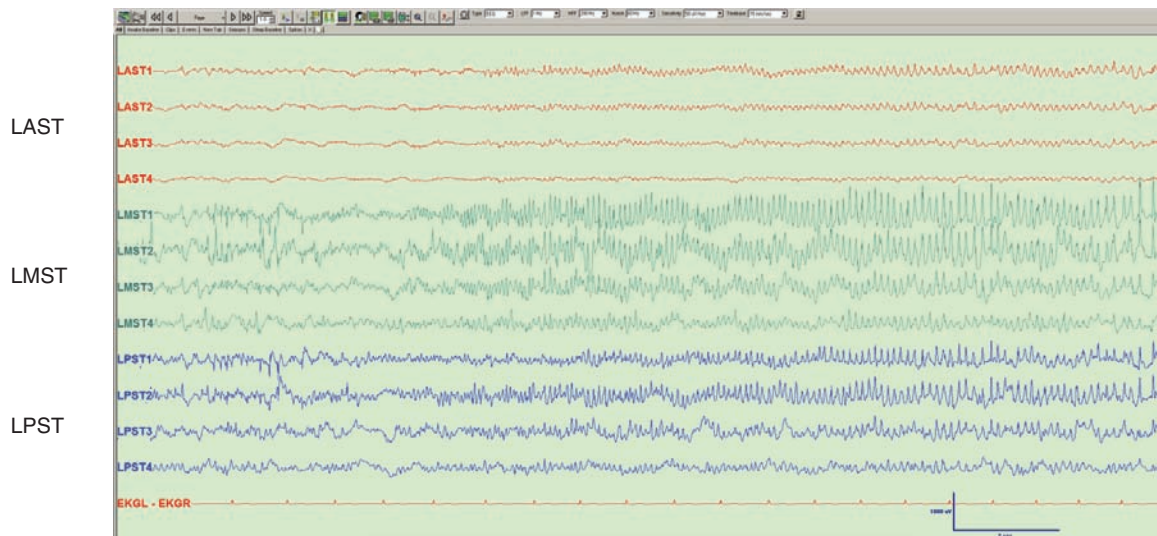


**FIGURE 18.8** Electrographic and clinical seizures from an adult patient with intractable seizures, nonlesional imaging, with electrodes implanted over the left temporal region. (A) Lateral skull x-ray showing implanted electrodes. An 8 × 8 grid (LTG) was implanted over the lateral temporal region. Three 1 × 4 strips (LAST, LMST and LPST) were implanted over the left subtemporal region (anterior to posterior). (B–D) Habitual clinical seizure (clinical onset at vertical line in B) showing onset with rhythmic 3–4 Hz sharp waves at LAST2–4 and LTG26, 32, and 42. (E–G) Electrographic only seizure starting at LMST1–3, LPST1–4, with rapid spread to LAST1–4. Patient had extensive resection of anterior and inferior temporal regions, including mesial structures, with resolution of her seizures.

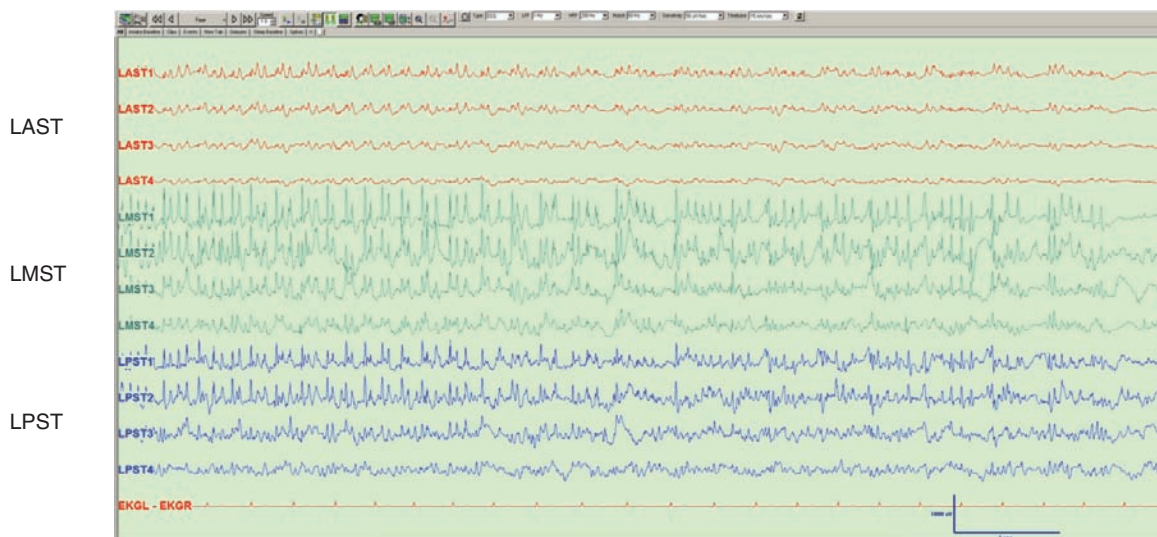




(D)



(E)



(F)

FIGURE 18.8 (Continued)



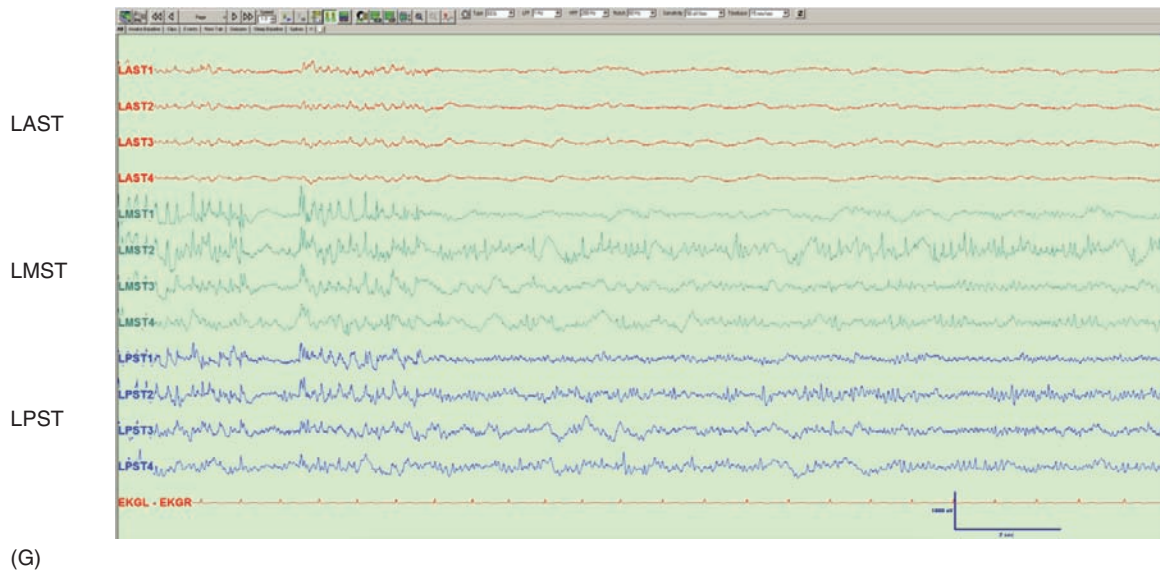
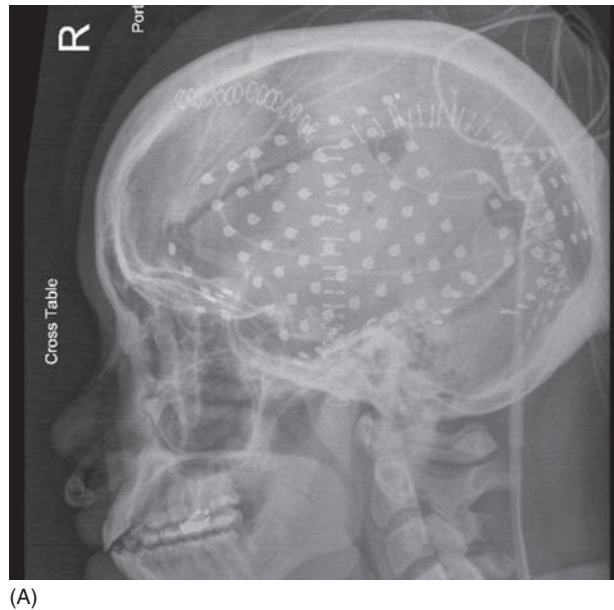
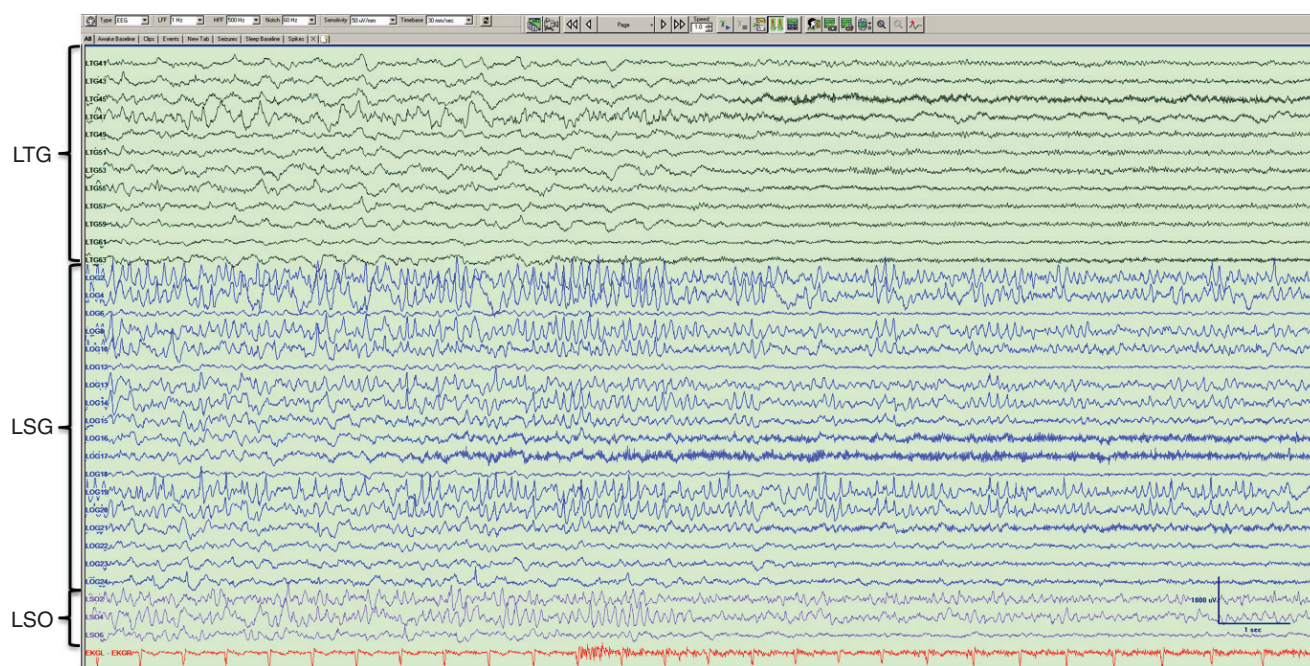


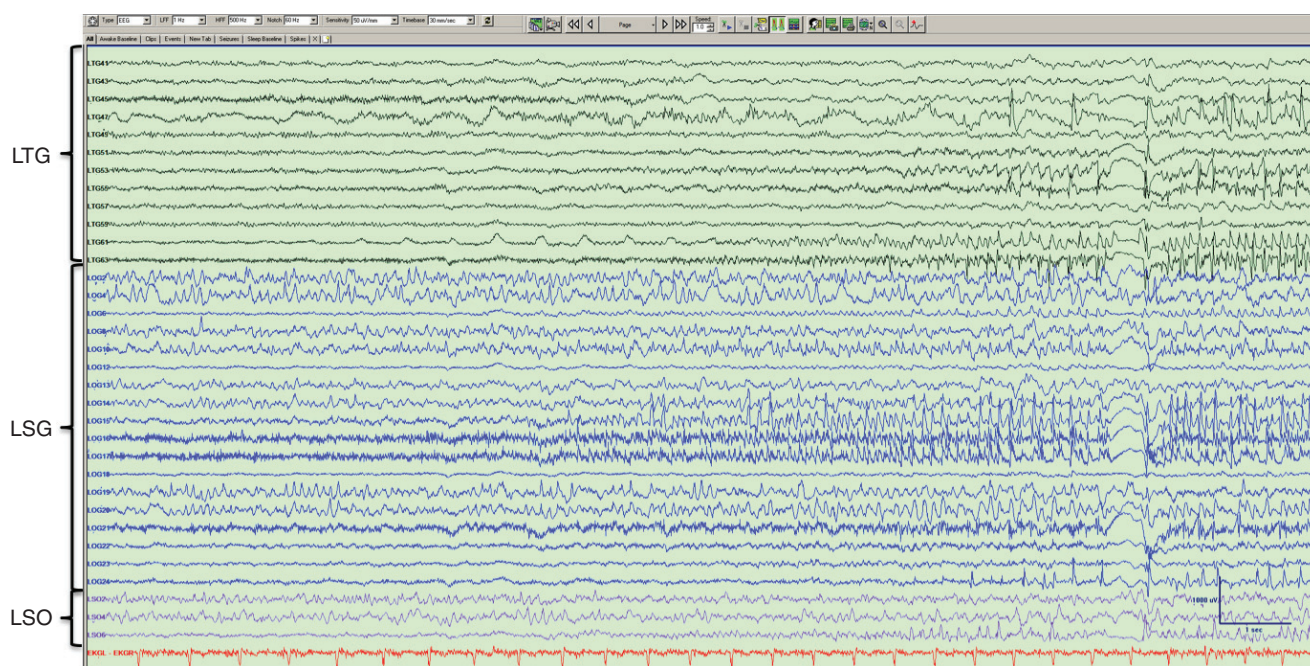
FIGURE 18.8 (Continued)



**FIGURE 18.9** Clinical seizures and brain mapping results from an adult patient with intractable seizures since childhood and nonlesional imaging. Scalp recording suggested a left temporal onset, middle/posterior. PET suggested a temporoparietal area of dysfunction. (A) Lateral skull x-ray showing implanted electrodes. An  $8 \times 8$  grid (LTG) was placed over the lateral temporal/frontal region and a  $4 \times 6$  grid (LOG) was placed over the posterior temporal/occipital region. Additional strips were placed over the orbitofrontal, subtemporal and inferior temporooccipital regions. (B–D). Habitual clinical seizure showing onset with high-frequency beta/gamma activity at LOG17, 16 with early spread to nearby electrodes (including LOG21–24, LTG45–47). Only a subset of electrodes is shown. (E) Results of brain mapping. A reconstruction of electrode location superimposed on the patient’s MRI is shown. Areas of seizure onset and early spread are circled. Auditory and visual naming sites were located immediately adjacent to the seizure onset zone. This limited the extent of possible resection—patient had no significant deficits after surgery and had worthwhile improvement in seizures but continued to have them.



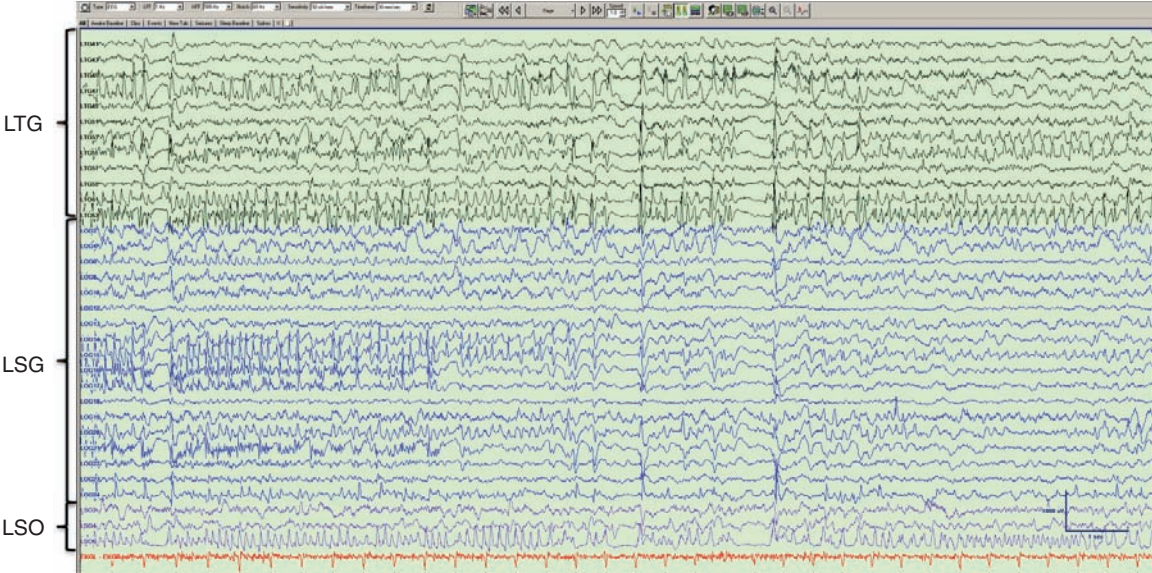
(B)



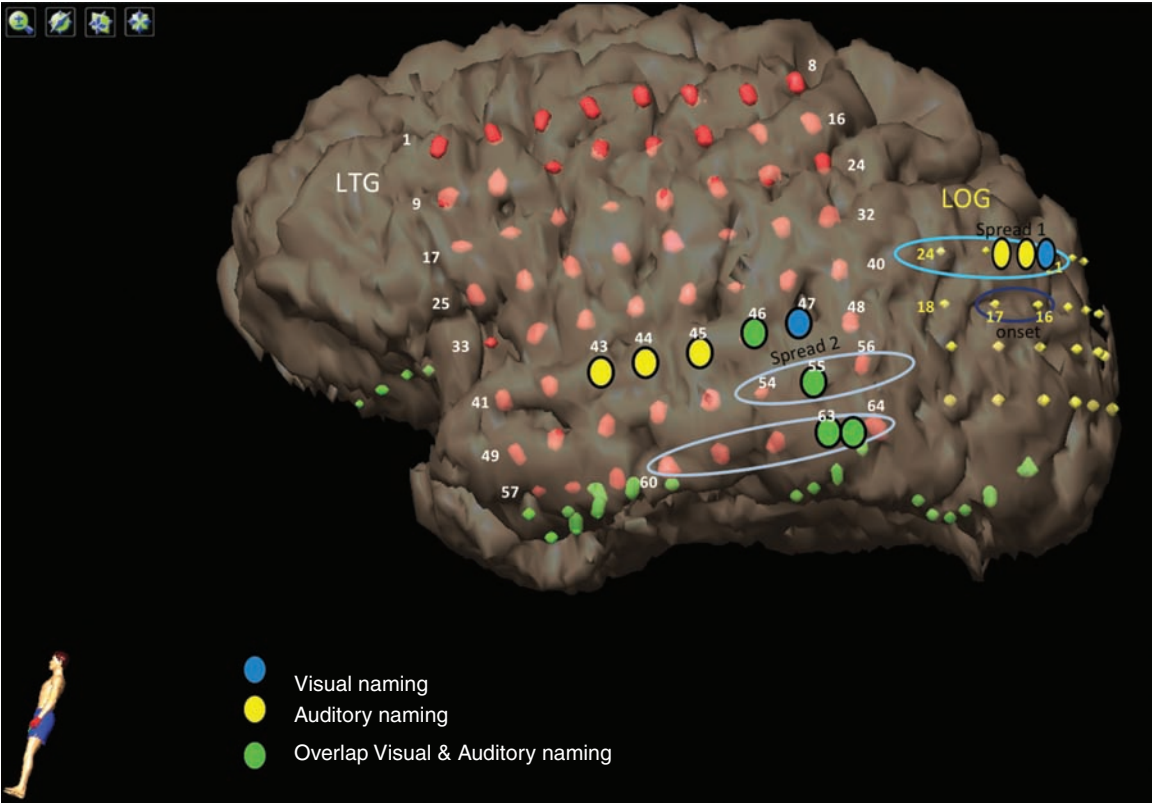
(C)

FIGURE 18.9 (Continued)





(D)



(E)

FIGURE 18.9 (Continued)

Intracranial EEG recording is an essential part of the epilepsy surgery evaluation for many patients with intractable seizures. It can help to localize the EZ and also assess its proximity to eloquent cortex. However, careful planning is essential to insure that the collected data are adequate. With attention to patient selection, planning, and interpretation of the data, intracranial monitoring may offer a significant chance for seizure freedom to patients who are intractable to medications and who cannot have surgery based solely on noninvasive evaluation.

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# Brain Mapping and Monitoring

*Sandra Serafini, Merlise Clyde, Aatif M. Husain, and Michael Haglund*

Either in the presence or in the absence of a lesion, once a patient with epilepsy is deemed a good candidate for resective surgery, they will often undergo preresection mapping to identify eloquent areas of cortex. Several techniques can be used, and the most common ones are cortical stimulation mapping (CSM) and central sulcus localization with somatosensory evoked potentials (SEP). Mapping of eloquent cortex allows the removal of maximum pathological tissue while simultaneously minimizing postoperative functional deficits in motor/sensory, language, or visuospatial abilities.

The organization of motor and sensory function was first described by Penfield and Rasmussen in a paper and schematics published in 1950 (Figure 19.1) (1). This description has been extensively relied upon to provide an expectation of the area of cortex devoted to specific motor or sensory functions, typically with good correspondence between anatomic landmarks and those respective functions in the normal population. It is not unusual, however, for motor and sensory areas to be displaced by a variety of pathologies, including epileptic foci and lesions (2,3), which introduce variability in exact functional locations from patient to patient.

Removing an epileptic focus or lesion is particularly challenging in the language-dominant hemisphere, because there is a lack of specific correspondence between anatomic landmarks and language beyond broad areas of perisylvian region such as inferior frontal, superior temporal, or inferior parietal gyri. Additional variability is likely to be introduced from an epileptic disorder, particularly with an early age of onset (4). While cortical areas necessary for motor, sensory, or language function are usually discreet (5), where a distance of only a few millimeters may be the difference between function or lack of function, the authors' experience is also consistent with reports of occasional "transition zones" where cortical stimulation induces only occasional word-finding disruption (6). Because of this combination of individual variability, variability due to pathology, and small, discrete functional areas, it becomes necessary to map out motor, sensory, and language areas for each patient to

create a tailored map from which the neurosurgeon can decide resection margins.

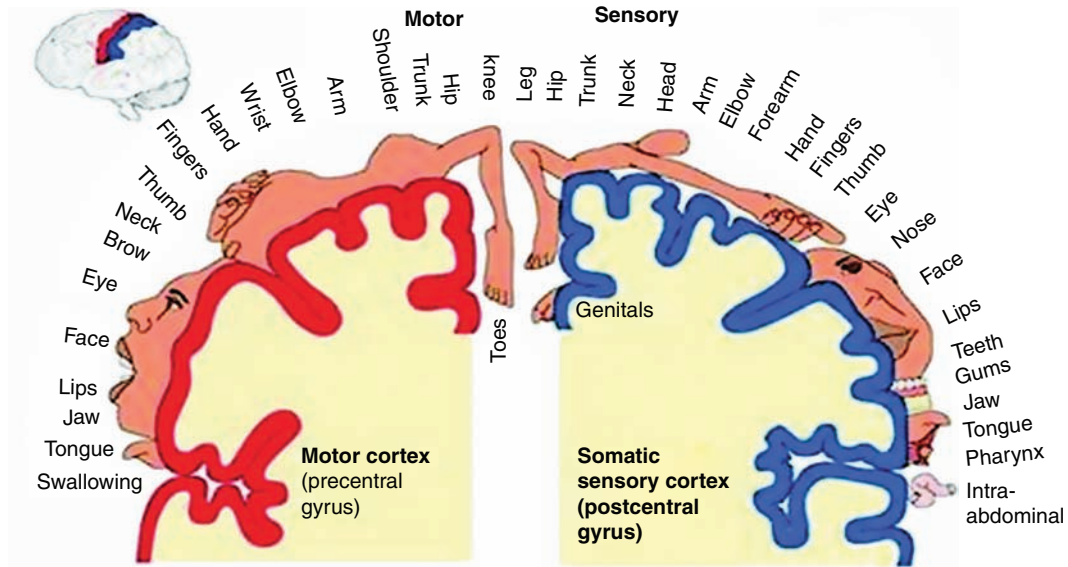
## CORTICAL STIMULATION MAPPING METHODS

### General Principles

There are two primary methods used for mapping function: (a) intraoperative and (b) extraoperative. Intraoperative mapping uses a bipolar stimulating electrode with an interelectrode distance of 5 mm (Ojemann Cortical Stimulator; Radionics, Burlington, Massachusetts). It is connected to a device that controls current amplitude, pulse-train duration for biphasic square-waves, and pulse frequency. Both the stimulator and device are shown in Figure 19.2.

Intraoperative mapping uses an "asleep-awake-asleep" method where the patient is put under deep sedation using IV propofol/remifentanyl (7) while the brain is exposed via craniotomy. Once the propofol is stopped, the patient is awake within 5 to 15 minutes (8). Local anesthesia is used for scalp discomfort and IV pain medication is used for dura discomfort. Most adults and pediatric patients 12 years of age and above are suitable for intraoperative mapping when given appropriate preoperative preparation and counseling.

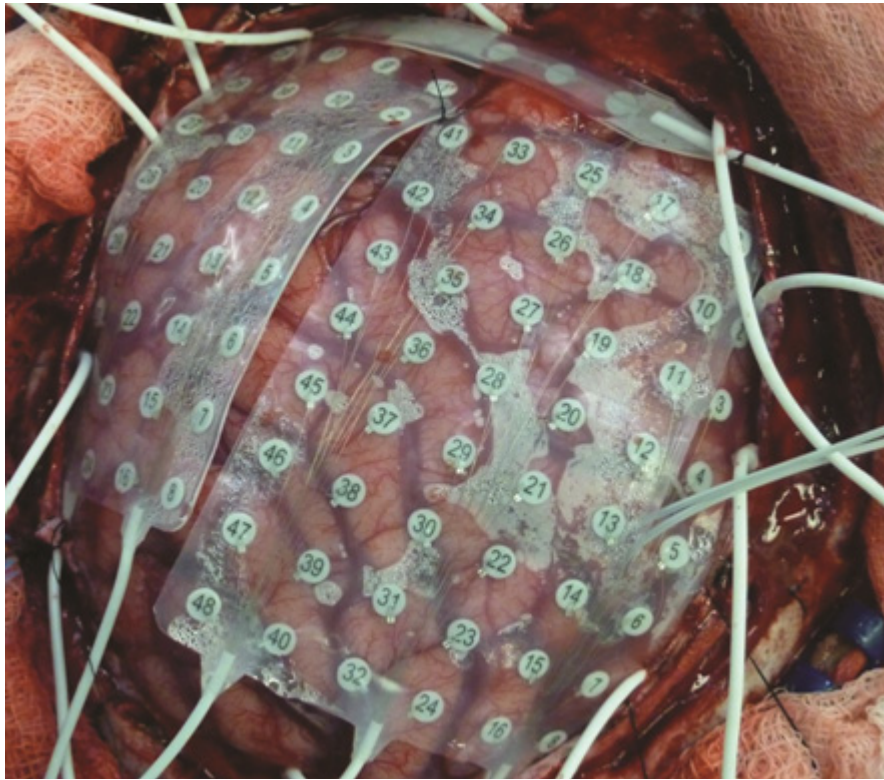
Extraoperative mapping uses a variable size grid electrode array that is placed subdurally on the surface of the cortex during a stand-alone procedure with the patient under general anesthesia. The grid is composed of a sheet (or strips) of electrodes embedded in a thin sheet of polyurethane, and within the grid are electrode discs made of a platinum alloy. Multiple grids or a grid and strip electrodes are used to aid in seizure and/or functional localization. Depth electrodes can also be placed within deeper structures of the brain to similarly aid in seizure localization. The entry point, trajectory, and depth of these electrodes are calculated by a computer to allow for precise placement. Grid and strip electrodes are 5 mm in diameter with center-to-center interelectrode distances of 1 cm (Ad-Tech, Racine, Wisconsin). Once the patient recovers from the grid placement procedure and



**FIGURE 19.1** Motor and sensory homunculus as described by Penfield and Rasmussen in 1950 (1).



**FIGURE 19.2** Bipolar stimulating electrode used for intraoperative mapping (top), stimulation on an exposed cortical surface (middle), the Ojemann Cortical Stimulator used to set pulse duration, pulse rate, and current level (bottom).



**FIGURE 19.3** Subdural grid arrays (4 x 8 and 6 x 8) side by side, with a 1 x 8 strip electrode placed superiorly on a brain's exposed cortical surface.

demonstrates seizure activity, brain mapping is performed at bedside. The mapping is done by applying a small amount of electrical current through a pair of electrodes to determine if any function is located directly under the space between the electrodes. Adult patients with neocortical epilepsy, or where the epileptic focus is unclear, in addition to pediatric patients under 12 years of age are generally candidates for the two-stage procedure that accompanies extraoperative mapping. A standard grid array is shown in Figure 19.3.

Current amplitude begins at 2 mA and progressively increases by 1 mA to a maximum of 14 mA to determine after-discharge (AD) threshold. ADs occur when cell populations continue to fire in synchronous bursts after the driving stimulation, such as from a bipolar stimulating electrode, has ceased (see Figure 19.4). A standard stimulation procedure in adults uses a biphasic square-wave pulse of 1 millisecond at 60 Hz and a maximum train duration of 4 seconds until AD activity is evoked or current amplitude reaches 14 mA. Pediatric patients generally require longer train durations and pulse durations to evoke motor movement, sensory effects, or to interrupt a language task due to immature neurophysiologic structures and connections. For extraoperative mapping, the AD threshold must be determined for each electrode pair. Variability in stimulating currents is generally higher for pediatric patients, but can also depend on the irritability or sensitivity of the underlying cortex. Though it is suspected that epileptogenic zones are more

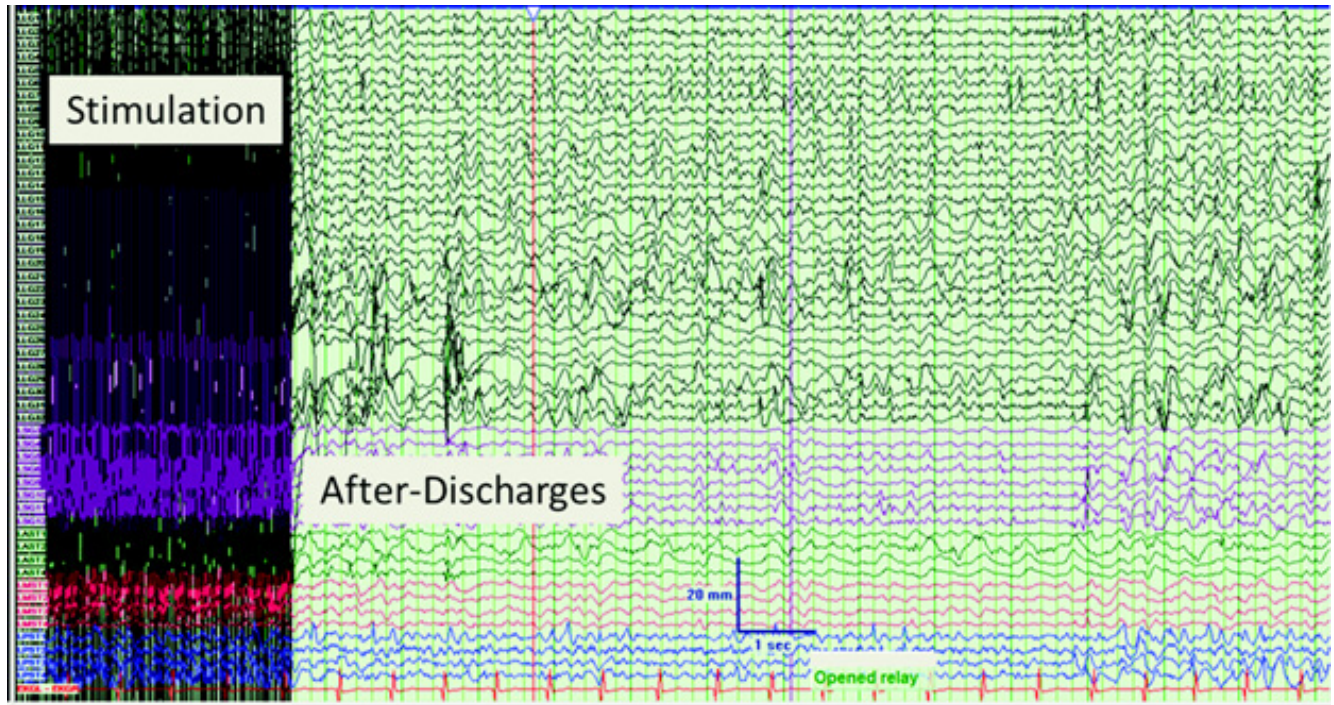
irritable or sensitive and therefore mandate lower stimulation currents, current research has yet to demonstrate this concept clearly (9,10). For both adult and pediatric patients, it is important to remain just under the AD threshold as repeated electrical stimuli that trigger ADs can eventually generate fully generalized tonic-clonic seizures. While intravenous (IV) medication can be provided quickly to a patient to stop this seizure activity (eg, lorazepam) (9), such an event usually prevents a mapping session from continuing until the following day. Tracking the start and stop of ADs is also important as they interfere with cognitive processing. During the language task of word-finding, for example, the authors have found that ADs raise the error rate, thus providing a potential false positive that may lead to preserving a cortical site unnecessarily, potentially at the cost of seizure control. Errors made during ADs are therefore given less consideration than errors made in the absence of ADs. Conversely, if a patient is able to give accurate responses despite the occasional presence of ADs, it can be inferred that the cortical site in question is not involved with that function.

## Mapping Paradigms

### *Motor and Sensory Paradigms*

Most commonly, mapping is done to localize motor, sensory, and language function. Mapping motor function entails applying an electrical stimulus and witnessing an overt but





**FIGURE 19.4** Electroencephalography during extraoperative mapping showing stimulation artifact and after-discharges following cessation of current application.

limited motor response such as movement in the jaw, face, thumb, hand, arm, foot, or leg. The patient may also feel their tongue move or a “twitching” in the back of their throat (pharyngeal area). Sensory mapping requires the patient to communicate a sensation in a specific location after the electrical stimulus has been applied. Typical dysaesthesias are transient sensations of tingling, tickling, prickling, pricking, or burning of the tongue, jaw, face, hand, arm, foot, or leg. For young pediatric patients who exhibit a great deal of movement at baseline, a brief but distinct calming or quieting effect can be seen when they experience a dysaesthesia, at which point the patient can be prompted to describe or show where they felt the sensation.

Speech-motor function should not be confused with language, though it is often found in the classic “Broca’s area,” ie, the operculum of the inferior frontal gyrus, but it is actually a motor function where the jaw, tongue, and face coordinate movement for articulation. It differs from motor mapping, in that the patient must perform a task that is then interrupted by the stimulation. This interruption is inferred to mean that the specific cortical site stimulated is necessary to perform the task. The tasks used for mapping this function are those that are highly overlearned, such as counting from 1 to 20, reciting the days of the week, or the months of the year. Errors noted are usually a generalized speech arrest, or the patient becomes temporarily dysarthric or apraxic, ie, they slur, stutter, or significantly lengthen the duration of the sound. Once the stimulation ceases, the patient is able to resume the task correctly. Current research from the authors

is consistent with investigations from the 1980s showing that across subjects, speech-motor cortical sites are found about equally distributed in the operculum of the inferior frontal gyrus and in the ventral portion of the precentral gyrus (2,11,12). If the patient has a slow-growing lesion in this region, it is also possible for the speech-motor area to reorganize perilesionally, occasionally separating into two distinct sites around the lesion, as seen by the authors and other investigators (13).

### *Language Paradigms*

Identifying language sites relies heavily on word-finding paradigms that use multiple input modalities, since dysnomia is a feature of virtually all aphasic syndromes; however, reading is also used as it represents an important function for resumption of postoperative academic or professional pursuits. The authors use the following paradigms: (a) visual object naming (V), (b) auditory naming (A), and (c) sentence completion (S). While visual naming (also referred to as confrontation or picture naming) has been the language task of choice since early the 1950s (14), it has become clear within the past decade that daily speech-based word-finding difficulties are seen following typical epilepsy resective procedures such as anterior temporal lobectomies when visual naming alone is used to map language (see Hamberger, 2007 and references within) (15). Word-finding errors in anterior temporal areas and the angular gyrus are best found using an auditory naming paradigm, while word-finding errors



in posterior temporal, anterior supramarginal, and middle frontal areas are best found using a visual naming paradigm. Reading errors are found most often in posterior supramarginal areas with a sentence-completion task (16). It is important to note that the discovery of a language site can depend heavily on the input modality; such distinct sites prompt the authors to routinely use all three word-finding paradigms to provide a comprehensive language map before resection.

All stimuli used for language mapping with each patient must be correctly named and/or read a minimum of two separate preoperative occasions, with removal of items not named correctly. This provision reduces the false positive rate as preoperative baseline errors can strongly resemble the types of errors induced by cortical stimulation. The aim is to have a very low or no baseline error rate during cortical mapping, with the vast majority or all errors being due to the stimulation itself. The patient is instructed to provide a carrier phrase prior to naming the object ("This is a ..." (visual/auditory naming) or "This says ..." (sentence completion)) to ensure attentiveness to the task and a nongeneral speech arrest. Stimulation is administered during two of every three trials on average, or can alternate between stimulation and no-stimulation. It is crucial that at least one-third of the trials is conducted without stimulation to enable the calculation of a nonstimulated baseline error rate, which is used to compare against site-specific error rates and, in turn, a clinically relevant language site. A 66% error rate at a given site is usually considered clinically significant for language.

Items are chosen pseudorandomly from pictures available in the public domain (17) or within the literature (16,18), based on the preoperative abilities of each patient. A balance of items from the semantic categories of "natural" and "constructed" is given, as research indicates deficits in the naming of living stimuli and famous faces appear to be vulnerable to anterior temporal lobe resection (19–21). Such deficits are consistent with the literature on proper name anomia (ie, famous people and places) being associated with anterior temporal lobe pathology (22,23).

### Bilingual Considerations

With bilingual or multilingual patients, CSM has long been used to identify cortical representations of each language. The experience of the authors is consistent with that of other investigators, who report that cortical sites may overlap across languages or be distinct to a specific language (24,25). Several factors must be taken into consideration when deciding to map a second language, the primary three being: (a) age of acquisition, (b) proficiency level of the second language, and (c) the nature of the languages (eg, alphabetic or idiographic), as each of these will influence the time devoted to mapping the second language as well as the tasks selected for mapping. For alphabetic languages, the three paradigms described earlier (visual naming, auditory naming, sentence completion) are designed with the assistance of a certified translator. For idiographic languages such as Mandarin,

additional ecologically valid tasks that incorporate tonal distinction (necessary for word comprehension and production) and idiographic recognition (necessary for reading) must be included to minimize postoperative language deficits.

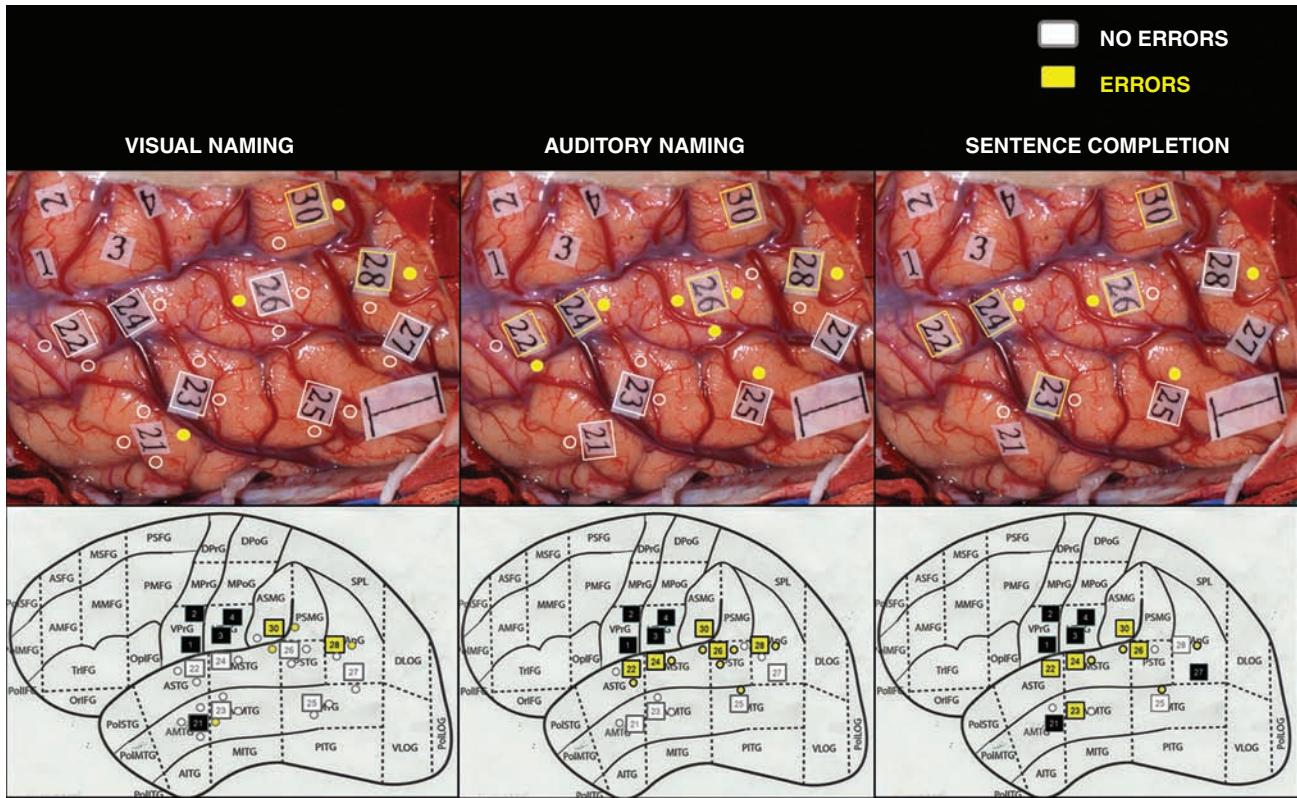
### Error-Coding

Standard error types in word finding include the following: (a) semantic paraphasias (substituting a related word, eg, "chair" for "table"), (b) phonological paraphasias (substituting a phoneme, eg, "bar" for "car"), (c) semantic/phonological blends (eg, "plane" for "train"), (d) off-target responses, ie, unrelated to the target word, (e) no-target responses (carrier phrase given but object not named), (f) perseverations within five trials, (g) apraxic errors, (h) phonological reductions (eg, "can" for "candle"), (i) neologisms, and (j) temporal delays. Error types for reading include: (a) slow/effortful reading (apraxic), (b) syntactic errors, (c) sentence-stem additions, (d) sentence-stem omissions, and (e) mixed sentence-stem errors (additions + omissions). Occasionally, a stimulation error will carry over to a subsequent nonstimulated trial either in the presence or in the absence of ADs. Such errors count against the baseline error rate, but are given less consideration than nonstimulated error trials.

### Localization and Analysis

Following either intraoperative or extraoperative mapping, the neurosurgeon will place sterile 5 mm<sup>2</sup> tags on the surface of the cortex, using a consistent numbering scheme to help localize essential areas (eg, 1–2 for motor areas, 3–5 for sensory areas, 10 for Broca's area, even-numbered 20s for the superior temporal gyrus, odd-numbered 20s for the middle temporal gyrus, and 30–33 for the supramarginal gyrus). Intraoperative photos are taken and used for subregion localization and group analysis. An example of intraoperative photos and subregion localization is shown in Figure 19.5.

Individual analysis immediately following a mapping session uses the Fisher's exact test to compare the trial error rates for the nonstimulated trials and the sequence of stimulated trials at a given site; rejection of the null hypothesis at a 60% error rate suggests that the location is a language site. For group analyses, the Fisher's exact test has limitations for comparing modalities across all patients because tests are not independent across subjects, ie, each site uses the same nonstimulated set of trials to provide a baseline, and the test does not allow one to incorporate other variables that may affect error rates. To determine subregional differences across modalities, hierarchical logistic regression models are fit to the trial error indicators. Such a model incorporates the varying number of stimulation and nonstimulation trials across modalities and patients and it is not necessary for stimulation sites to be repeated across modalities within patients nor is it necessary to have an equal number of stimulation and nonstimulation trials across modalities or across patients.



**FIGURE 19.5** Intraoperative naming sites in word-finding paradigms used to map language. Error-free stimulated sites (white), stimulated sites with error trials (yellow), sites not stimulated for language (black).

**Abbreviations:** VPrG, ventral precentral gyrus (motor strip); VPoG, ventral postcentral gyrus (sensory strip); Prefixes A=anterior, M=middle, P=posterior, Suffixes STG=superior temporal gyrus, MTG, middle temporal gyrus; ITG, inferior temporal gyrus; SMG, supramarginal gyrus; AnG, angular gyrus; 1-cm indicator shown in posterior/inferior corner of digital photos.

**Source:** From Ref. (16). Serafini S, Clyde M, Tolson M, Haglund M. Multimodality word-finding distinctions in cortical stimulation mapping. *Neurosurgery*. 2013;73:36–47.

## Postoperative Language Follow-up

Studies that address postoperative language function typically assess postoperative language changes as it relates to removing or how close a resection has come to an identified site. There are very few reports on language function following the removal of visual naming sites as it was the standard of care since the 1950s to preserve those sites. The most widely accepted view of how proximate a resection can get to a visual naming language site before persistent deficits are incurred is approximately 1 cm (26), with increasing evidence that removing auditory naming sites affects postoperative naming in both visual and auditory domains (27).

## Limitations

There are several advantages of using CSM to provide tailored motor, sensory, and language maps, particularly its ability to test a small, discrete area of cortex that likely mimics the effect of resection. Still, there are limitations that are recognized across epilepsy surgical centers, including: (a) the need for a high level of patient cooperation, (b) limited

ability to stimulate sulcal areas, (c) the need for short yet ecologically valid language tasks, (d) low AD thresholds potentially rendering false-negative sites essential for language.

## SOMATOSENSORY EVOKED POTENTIAL MAPPING

### Rationale

SEP mapping is performed when the central sulcus needs to be identified. This is typically done when the suspected epileptogenic lesion lies close to motor or sensory areas. Though the central sulcus can often be identified by direct observation, when there is nearby pathology, such as a brain tumor, it can become distorted and visual identification may be inaccurate.

### General Principles

The hand area has a large representation on the somatosensory and motor cortices. Consequently, median nerve stimulation is performed and cortical evoked potentials are



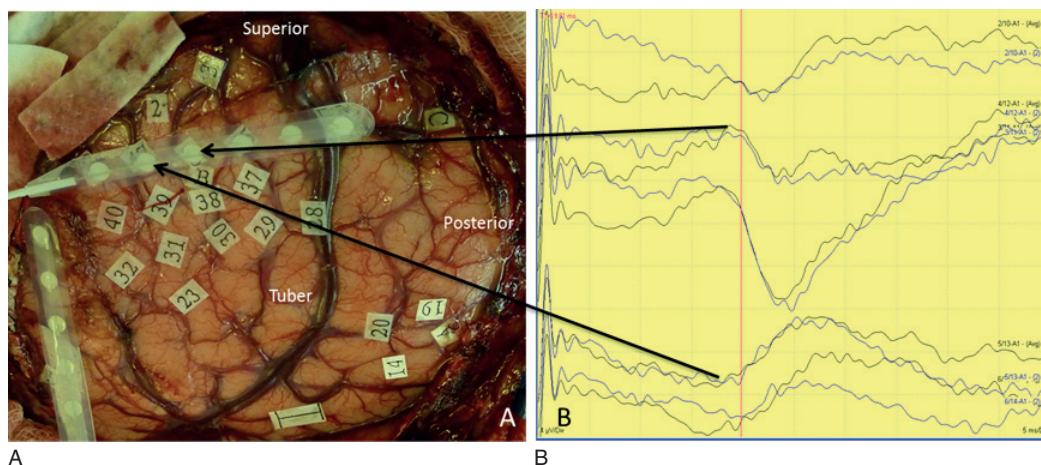
recorded. Median nerve stimulation generates a cortical EP (N20 potential) over the somatosensory cortex. Concurrently, a positive potential is also generated over the motor cortex. The latency of this potential often occurring a little later is called the P22 potential. There are various theories that explain why a P22 potential is generated with median nerve SEP. The most commonly accepted one suggests that while most somatosensory fibers relay from the ventral postrolateral nucleus of the thalamus to the somatosensory cortex, some also relay to the motor cortex in the hand area. Hence, in addition to the N20 potential recorded from the somatosensory cortex, a P22 potential is recorded from the motor cortex. When the median nerve SEP is recorded from a series of electrodes perpendicular to the central sulcus reference to a distant site, a pseudo “phase reversal” between the N20 and P22 potentials will be noted.

### Technique

Stimulation of the median nerve is performed the same way as is typically done for median nerve SEP monitoring. Instead of scalp recordings, however, a subdural strip (or sometimes grid) electrode is used for recording. The strip electrode, usually six to eight contacts, is placed perpendicular to what is assumed to be the central sulcus. Each of the strip contacts is referenced to a distal electrode, which is usually placed on the contralateral mastoid or ear. In this manner, a referential recording is obtained. A reliable response is usually seen within 50 to 100 repetitions. As noted earlier, an N20 potential is seen over the somatosensory cortex, while a P22 is seen over the motor cortex (Figures 19.6A and B). Depending on how the strip contacts are connected to the amplifier, a pseudo “phase reversal” or pseudo “positive phase reversal” will be seen. If the strip

electrode contacts over the somatosensory cortex are in the lower amplifier channels (1–3), a positive phase reversal will be seen as the N20 will be toward the top of the screen and the P22 toward the bottom of the screen. If the contacts over the motor cortex are in the lower amplifier channels, the P22 will be on the top of the screen and the N20 will be below it, creating a “negative” phase reversal. The strip electrode can be moved to different locations to see if a better phase reversal can be identified (ie, electrode will be closer to the hand area). The central sulcus can also be traced from the vertex area along the lateral convexity of the cortex by progressively moving the strip electrode caudally and identifying successive sites where a phase reversal is noted.

Mapping eloquent cortex with CSM and median nerve SEP are helpful in maximizing the area of brain that can be safely resected. In the language-dominant hemisphere, using CSM to identify motor, sensory, and language areas remains the gold standard to prevent or minimize postoperative functional deficits. There is considerable individual variability in the exact location of language sites, making it essential to provide a tailored map for each patient. While word-finding appears to have become a validated and predictive indicator of postoperative language function, it is necessary to vary the input modality of a word-finding task to obtain the totality of distinct language sites and thus provide a comprehensive language map to the neurosurgeon. Such a comprehensive map will allow for the best balance between achieving seizure freedom and minimizing postoperative deficits in motor, sensory, or language functions. Median nerve SEP mapping can supplement CSM in localizing the central sulcus and motor and sensory cortex.



**FIGURE 19.6** This figure shows a 6-contact strip electrode placed directly on the cortex (A). The superior and posterior aspects of the brain are labeled, as is the tuber, which has been identified as the epileptogenic zone and is to be resected. Median nerve stimulation produced the responses noted (B). Notice the N20 (upper arrow) and the P22 (lower arrow). This represents a “positive phase reversal” as the N20 and P22 face away from each other. The central sulcus lies between contacts 3 and 4.



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# Structural Neuroimaging

*Matthew W. Luedke and William B. Gallentine*

Clinical localization is one of the hallmark skills of a neurologist. Seizure semiology is an elegant method of localization, and the positive symptoms of an epileptic lesion are focal cortical functions made manifest. EEG is a physiologic tool of localization, permitting a skilled neurophysiologist to identify functional abnormalities and their rough anatomic locus.

Despite the utility of clinical and physiologic localization, anatomic localization is a critical tool for the diagnosis and management of epilepsy, at all stages of patient management. Neuroimaging by CT and MRI has revolutionized the physician's ability to identify both normal and abnormal anatomy. Whether it is a CT scan to rule out an acute neurologic emergency after a first seizure or a high-definition MRI to demonstrate a subtle cortical dysplasia, neuroimaging can play a vital role in the assessment of epilepsy. Particularly in complex epilepsy cases, the presence and location of anatomic abnormalities can govern the location and size of a surgery, or even whether a surgery can occur. The mere absence of a lesion in otherwise clinically and physiologically focal epilepsy can have dramatic prognostic implications (1).

This chapter will examine anatomic imaging in epilepsy, beginning with the basic history of neuroimaging. Next, the physics of CT and MRI and the limitations this imposes on their clinical use will be discussed. Thereafter, the clinical utility of CT versus MRI in general will be reviewed. The value of neuroimaging in evaluation of the acute seizure and in established epilepsy will then be noted. Finally, the common abnormalities seen on neuroimaging in patients with epilepsy will be discussed.

## HISTORY

The history of medical imaging can be traced back to Wilhelm Rontgen. In 1895, Rontgen identified the x-ray, a high-frequency band of electromagnetic radiation lying between the ultraviolet and gamma range. During his investigations, he discovered that x-rays could be captured

on film, and moreover, a limb interposed between the x-ray emitter and the film would generate a shadow image of underlying bones. This discovery rapidly found its way into the hands of physicians, leading to the birth of both diagnostic and therapeutic radiology. For his efforts, Rontgen was awarded a Nobel Prize, the first of many awarded to pioneers in medical imaging.

Early radiographers faced a challenge when it came to neuroimaging: the brain is radiolucent, and of a relatively uniform density. Unlike bone imaging, where the organ of interest is radiopaque, or thoracic imaging, where air and fluid levels and differential organ densities allow for resolution of adjacent structures, the plain-film of the head is limited to an evaluation of the skull (2).

In 1918, Walther Dandy adapted the air-contrast abdominal film to x-ray imaging of the human brain. He developed a technique to insufflate air into the thecal sac, and then distributed it throughout the CNS. The introduction of air into the ventricles and the subarachnoid space permitted rudimentary resolution of large brain structures. If sufficiently outlined by air, and if adjacent to contrasting structures, pneumoencephalography could identify large brain lesions, though the sensitivity and specificity were poor. Nonetheless, some sources suggested that CNS tumor diagnosis rates increased by as much as 33% with the use of pneumoencephalography (2).

Advances in pneumoencephalography occurred through the 1960s, with the ultimate evolution involving chairs that flipped patients after insufflation, allowing for the even distribution of air into the ventricles, cisterns, and subarachnoid space. Nevertheless, resolution remained poor. Beyond the limited resolution, the pneumoencephalogram was notoriously painful; its reputation was so frightening, it made its way into popular culture as an act of medical futility in the 1973 horror film, *The Exorcist* (2).

Content with neither the resolution nor the comfort of the pneumoencephalogram, researchers looked for an alternative. Beginning in the 1960s, three separate investigators, William Oldendorf, Alan Cormack, and Godfrey

Hounsfield, were working on techniques for cross-sectional x-ray imaging. In 1961, Oldendorf was the first to create a functional cross-sectional imaging device that he cobbled together from household parts, and obtained a patent for his creation. Yet, in one of medical history's most notorious oversights, x-ray manufacturers roundly rejected his project.

Shortly after Oldendorf's rejection, Cormack devised an algorithm for tomographic reconstruction, and by the early 1970s, Hounsfield helped devise the first commercially successful CT scanner for the British device company, EMI, Ltd. Despite their similar efforts, Cormack and Hounsfield were unaware of Oldendorf's creation. In 1979, Cormack and Hounsfield won the Nobel Prize in Medicine, leaving Oldendorf unrecognized, and largely forgotten (2).

The first clinical EMI scanner was used for clinical trials in 1971 to 1972 at the Atkinson Morley Hospital of London, England. In 1973, the first North American scanner was installed at the Mayo Clinic in Rochester, Minnesota. The first units had a resolution of  $80 \times 80$  pixels of approximately  $3 \text{ mm} \times 3 \text{ mm}$  resolution, with slice widths of between 8 mm and 13 mm. The scans were time consuming and radiation intensive. But even with these limitations, the scanner was revolutionary. A contemporary of the first Mayo Clinic EMI scanner wrote, "As I saw the images it was obvious that, despite some streaking on certain sections caused by patient motion, the system was capable of displaying with remarkable clarity many pathologic processes involving the brain, including tumors, infarcts, hemorrhages, and infectious processes" (3–5).

In the ensuing four decades, CT resolution has improved, acquisition time has decreased, and radiation exposure has decreased. Moreover, advances in computer technology allow clinicians to create complicated reconstructions.

In contrast to the CT, the MRI is based off of a younger technology. Nuclear magnetic resonance (NMR) was developed in the 1940s as a tool for chemists, using powerful magnets to generate characteristic radio-frequency emissions from atomic nuclei. Initially a laboratory tool used on small chemical samples and requiring small and powerful magnets, its clinical application was less apparent and more difficult than that of early x-rays. While it took Rontgen a matter of weeks to start experimenting with x-rays for medical use, it took over 20 years for the first attempt to use NMR scans on laboratory animals. The first human imaging was performed in 1977, and the first brain imaging was published in 1980, the same year the first clinical scanners were released. Early scanners were limited to T1 and T2 sequences, and contrast by gadolinium was only FDA approved in 1988. Yet, even the early 1.5T scanners could provide better contrast between gray–white matter structures than contemporary CT scanners, and rapidly became a staple in the evaluation of neurologic disease. As with the CT scanner, the impact of MRI was so profound that Paul Lauterber and Sir Peter Mansfield, early pioneers in the clinical application of NMR, were awarded the Nobel Prize in medicine in 2003 (2).

As with CT scanners, MRI has undergone an evolution since its initial clinical debut. Clinical 3T scanners are now common, and several institutions have 9.4T MRI scanners for clinical research purposes. In addition to advances in magnet power and resolution, different pulse sequences have been developed to assess for different anatomical structures.

## PRINCIPLES

CT and MRI rely on different technology to render anatomic imaging. An appreciation for the basic physics involved in these systems, along with the technology, nomenclature, and potential pitfalls, is vital to their appropriate implementation in the clinical setting.

The CT scan relies on x-ray spectrum electromagnetic radiation. X-rays consists high-energy ionizing photons, with frequencies faster than that of ultraviolet radiation, but still lower than that of gamma radiation. Shorter wavelength x-rays are considered "hard," and can penetrate objects, and these are the x-rays that are used in medical imaging.

Clinical x-rays were traditionally resolved on film. As photons from an emitter passed through a patient, tissues of differing density and composition would either absorb or diffract x-rays in transit. Radiopaque objects like bone or dense organs absorb or diffract more photons, whereas radiolucent structures, such as fluid or air, would allow greater pass-through. The photons would then strike a plate of film, with areas behind radiolucent structures receiving a greater exposure. When developed, areas of lower photon exposure would appear brighter, and higher photon exposure would be dark, creating a two-dimensional shadow of a three-dimensional object (6).

Instead of creating a two-dimensional shadow of a three-dimensional form, CTs generate tomograms. A tomogram is two-dimensional cross section of a three-dimensional object. The advantage is twofold. First, a cross-sectional slice is, by nature, a two-dimensional image and there is less data lost than there is in the rendering of a three-dimensional object into a two-dimensional shadow. Second, by combining a series of cross-sectional samples, an imager can reconstruct three-dimensional relationships in a subject.

To generate a tomogram, a CT scanner uses x-ray detectors as opposed to film. Instead of a wide-angle x-ray emission, the x-ray tube is calibrated to produce a narrow beam. This emitter is mounted in a ring, opposite either a single x-ray detector, or a detector array. To generate an image, an object is placed in the ring, and successive exposures are made in the plane of the ring at different angles. Each exposure will vary, depending on the density and radiopacity of the tissues along that vector. With each successive exposure, the detector records the energy of the incoming x-rays, determining the absorption of the radiation along that path, its attenuation coefficient. Using a variety of algorithms, a computer collects a map of linear attenuation coefficients from a given cross-sectional plane. To generate an image, these values are then converted to Hounsfield scale and mapped onto a two-dimensional screen. The Hounsfield scale, measured



in Hounsfield Units (HU), is calibrated so that the linear attenuation coefficient of pure water and atmospheric air at standard temperature are zero and -1000, respectively (6).

Because CT scans rely on the differential attenuation of x-rays to generate images, they best resolve adjacent structures with dissimilar radiopacity. It is possible to create dissimilar opacity by introducing contrast agents—radiopaque fluids that can magnify the density of a natural fluid space. Typically iodinated contrast agents are used in contemporary CT scans, and they can be injected into the blood stream to contrast arterial or venous systems, or, less frequently, into the CSF. The contrast can highlight vascular structures and regions of increased vascular permeability.

The use of x-rays carries risk, and CT scanners can emit significant doses of ionizing radiation. While a typical plain-film x-ray can emit 0.01 to 0.15 Gy of radiation, a CT scan can emit 10–20 Gy. An average annual exposure for a human in the United States is 2.4 Gy; clearly, CT scans represent an exposure beyond baseline (7). Repeated CT scans, which can occur in prolonged hospitalizations during critical illness, multiply that exposure. This cumulative radiation dose represents a cancer risk, and this risk is magnified in younger patients. While the overall lifetime risk of developing a terminal cancer from a single CT scan is estimated at 1:10,000, the risk increases to 1:1000 for a 1-year-old (8). Taken individually, the risk is small, but repetitive imaging carries a nonnegligible risk.

Professional organizations have created campaigns to encourage strategies for generating high-quality imaging while minimizing radiation exposure. The *Image Gently Campaign*, directed toward pediatric patients, and *Image Wisely Campaign*, for adults provide best practice guidelines to reduce radiation exposure.

In addition to the radiation, the use of iodinated contrast agents can present a risk. Acute kidney injury can be a side effect of iodinated contrast, and is most likely to occur in patients with preexisting kidney injury. Contrast agents can also lead to allergic reactions, ranging from fevers and flushing to overt anaphylaxis. Modern low-osmolar contrast agents are less provocative than older agents. However, caution must be used whenever contrast is considered (6).

MRI is a larger-scale implementation of the analytic chemistry technique of NMR spectroscopy. When exposed to a powerful oscillating magnetic field, the protons of certain atomic nuclei can be brought into alignment (for the purposes of MRI, the atoms of interest are  $^1\text{H}$ ). When the magnetic field is removed, those protons relax into their equilibrium state, releasing the energy as a photon with a characteristic radio-range frequency at a predictable rate of decay. The relationship of the atom to its surroundings, or lattice, can also change that frequency and its emission time (6).

When coupled to a radio receiver of sufficient sensitivity, the signal from these radio-frequency emissions can be collected. In the clinical MRI, adjustments in the orientation of the oscillating magnetic field can generate spatial information from the radio emissions. Likewise, adjustments in

the timing of the sampling from the radio receiver can help specify what kinds of tissues generate the most signal. The mixture of spatial data and signal density is coupled to form an image map, which can either be acquired tomographically, in axial, sagittal, and coronal sections, or volumetrically, where the whole volume of MRI data for an object is acquired. This 3D volumetric data can be reconstructed into coronal, axial, and sagittal sections, or even curvilinear representations. The combination of magnet and radio detection parameters are referred to as sequences. The two primary clinical MRI sequence types are T1, which favors signal from fat-rich tissues, and T2, which favors signal from water-rich tissues (Table 20.1) (6).

In addition to T1 and T2, other imaging sequences have been created. One common sequence is T2-FLAIR (fluid-attenuation inversion recovery), which preserves the strong T2 signals while eliminating the excess T2 signal derived from large collections of CSF (Table 20.1). Sequences such as susceptibility weighted imaging, or gradient echo, can pick up subtle differences in magnetic susceptibility, making it useful for identifying hemorrhages or blood vessels. Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences track the movement of water, and can identify areas of restricted fluid movement, such as infarcts or cystic structures (Table 20.2). Diffusion tensor imaging (DTI) is a related sequencing system that follows diffusion along tissue tracts, and can help identify white matter pathways. These are among the most common imaging sequences in use, and represent the bulk of those employed in the diagnosis and management of epilepsy (6,9,10).

Like the laboratory NMR spectrograph, the clinical MRI relies on a cylindrical electromagnet, though open MRIs exist, but have a different manner of construction. The magnet coil must be super-cooled for proper function, and this is accomplished with an insulated reservoir of liquid helium. Clinical machines must be large enough to hold an adult human, and are generally of proportionally lower power than their smaller relatives. When a subject is placed in the bore of the MRI, a framework containing a second coil, which is the receiver for the radio-frequency emissions, surrounds the structure of interest. To improve the signal-to-noise ratio, the MRI is installed in a radio-shielded suite, minimizing environmental radiation contamination.

MRI, as with CT, is amenable to contrast enhancement. MRI contrast media is typically made with gadolinium, a paramagnetic transition metal that shortens the relaxation time of nuclei. This creates a prolonged T1 signal, generating a brighter image on T1-based sequences. Like CT contrast, gadolinium contrast agents can be administered intravenously. It can highlight large vessels in angiography or venography, regions of high vascularity, such as angiogenic tumors, and regions of inflammation (6).

Gadolinium contrast enhancement is not without risk. In patients with significant renal impairment, it has a risk of causing nephrogenic systemic fibrosis (NSF), a disease process similar to scleromyxedema or scleroderma, with skin fibrosis, joint contractures, and even fibrosis of visceral organs. It appears

**TABLE 20.1 Common Signal Intensities on T1, T2, and FLAIR Pulse Sequences**

PULSE SEQUENCE	HYPERINTENSE STRUCTURES	HYPOINTENSE STRUCTURES
T1	White matter Deep nuclei High-fat-density masses Brainstem Corpus callosum Calcium	Gray matter Water, CSF, vitreous Hemosiderin
T2	Water, CSF, vitreous Gray matter Edema Low-fat-density masses	White matter Deep nuclei High-fat-density lesions Flow-voids Corpus callosum Hemosiderin
FLAIR	Gray matter Edema Low-fat-density masses	White matter Deep nuclei High-fat-density lesions Water, CSF, vitreous Flow-voids Hemosiderin

**TABLE 20.2 Common MRI Pulse Sequences and Their Utility in the Evaluation of Epilepsy**

PULSE SEQUENCE	UTILITY
T1	Assessment of general anatomy Common pre- and postcontrast comparison study
T2	Pathology “workhorse” scan Excellent for edema, scarring, mass lesions
T2-FLAIR	Similar to T2 Hyperintensity is criterion for MTS
DWI/ADC	Excellent for strokes Evaluating masses
SWI/GRE	Identification of blood and blood metabolites Evaluation of large and medium vessels
Spectroscopy	Evaluation of metabolic dysfunction Assessment of masses unamenable to biopsy
DTI	Assessment of lesion connectivity Identification of some masses Evaluating success of callosotomy

to be related to certain linear chelates of gadolinium administered in patients with advanced renal disease. The advent of macrocyclic agents like gadoteridol and gadobutrol, along with restricted use in renal disease, has reduced the risk of NSF (11).

MRI, overall, is considered a safe imaging modality. The most significant danger is posed by the magnetic field. Patients have been injured and killed when ferromagnetic objects were captured by the MRI magnetic field and propelled into the scanner’s aperture. Likewise, patients with

ferromagnetic implants or devices may not be able to receive MRI scanners. With appropriate safety measures, this risk can be minimized, and device makers are making many of their implants, such as pace makers, MRI compatible (12).

## NOMENCLATURE

The language of CT imaging is that of relative density. Brighter structures, those with higher relative attenuation of the x-ray beam, are described as hyperdense. Darker structures, those with a lower relative attenuation, are hypodense. Structures that are of similar density are labeled isodense. Structures with very high Hounsfield unit values are sometimes referred to as radiopaque, while very low value structures are infrequently referred to as radiolucent. If a structure demonstrates a higher density after the introduction of a contrast agent, that structure can be described as enhancing. In the authors’ experience, the term “enhancing” is often used in error to mean “hyperdense”; this is a potentially confusing error, as true contrast enhancement can have significant clinical implications.

MRIs are described in terms of relative signal intensity in a given sequence. Bright spots on an image are hyperintense, dark spots are hypointense, and regions of comparable brightness are isointense. However, it is critical to note the sequence when making these descriptions, because signal intensity can vary dramatically. For example, a ventricle on T2 will appear hyperintense, but the same fluid space on T1 or T2-FLAIR will appear hypointense relative to its surroundings. Hyperintensity is sometimes referred to as signal prolongation. As with CT, it is important to reserve enhancement to describe regions of a given sequence that are brighter after the addition of contrast than on a precontrast scan.

## GENERAL COMPARISONS

CT and MRI scans have their strengths and weaknesses, and together are complementary technologies. CT scans are rapid and clearly resolve tissues with very different densities. This makes them excellent for emergent imaging. CTs can, for example, clearly demonstrate acute extravascular blood in the brain, as it has a markedly higher attenuation coefficient than surrounding tissues or CSF. Likewise, bony injuries or regions of severe edema can be identified easily. CTs are also a good gross anatomy scan, able to identify mass effect, herniation syndromes, or large tissue deficits like old infarctions or regions of sclerosis and atrophy. Calcifications are also very visible on CT scans. They are poor, however, at differentiating similar tissues, such as gray and white matter, and they do not pick up the subtleties of cortical or nuclear structure. CTs can easily miss cortical dysplasia, small tumors without significant mass effect, and areas of subtle sclerosis or scarring. The addition of contrast can help identify blood vessels, vascular tumors, and inflammatory lesions, but it cannot improve gray–white matter differentiation or add significant detail to the overall brain anatomy. CT scans also carry with them the risk of radiation exposure, which is a particular consideration in the young (6,9).

MRI scans better resolve gray–white matter differentiation than CT scans, and other tissues that are structurally dissimilar, but have similar radiopacity. They are better at identifying tissue abnormalities. By using T2-derived sequences, MRI is particularly apt for demonstrating high water content lesions such as white matter tract injuries, encephalomalacia, cystic structures, and edema. The ability to generate coronal imaging without reconstruction is also a powerful tool, especially for examining temporal lobe anatomy, which is less visible in axial imaging. MRI with contrast can further demonstrate inflammatory changes and vascular tumors. Bone and calcium deposits can be seen on MRI, but they do not stand out as well as they do on CT. MRIs also do not carry the radiation exposure of CT. It is, however, significantly slower, and scans using multiple sequences can last over an hour. MRIs are also limited to patients without ferromagnetic implants. From a fiscal perspective,

MRIs are more expensive than CT, and elective MRI may require special permission from insurance providers or be cost-prohibitive for the uninsured. Moreover, CT scanners are available in more hospitals than MRIs, and may be the only available structural imaging (Table 20.3) (6,9,13).

## CLINICAL APPLICATIONS

In this section, the neuroimaging recommendations for first-time seizure and established epilepsy or medication resistant epilepsy will be discussed. Thereafter, the common CT and MRI findings that may be seen in patients with epilepsy will be noted.

### Neuroimaging Recommendations

Anatomical imaging in the setting of a first-time seizure has two purposes. The first is the emergent assessment for provocation. Many neurological emergencies can provoke seizures in the acute phase, including, though not limited to traumatic injury, hemorrhages and hematomas, infarctions, tumors, and infections. While often accompanied by focal neurologic deficits or other findings suggestive of a critical illness, the physical examination can often be limited by postictal somnolence. Even if the patient is neurologically intact at the time of evaluation, the fact that the patient had a seizure raises the pretest probability of an anatomic abnormality; the yield of imaging in a first-time seizure is approximately 10% (9,14).

The second indication for anatomic imaging is prognosis. Epilepsy is traditionally recognized as a syndrome of recurrent and unprovoked seizures, though epilepsy is also recognized as a single seizure accompanied by findings that significantly raise the likelihood of recurrence. One such finding is abnormal neuroimaging, which yields a hazard ratio for seizure recurrence of 2.44 (95%CI 1.09, 5.44) over 4 years. The 2015 American Academy of Neurology (AAN) guidelines for the medical management of a first unprovoked seizure recommend that abnormal neuroimaging be included in decision making about the initiation of antiepileptic medications after a first-time seizure (15).

**TABLE 20.3 A Comparison of the Clinical Utility of CT and MRI**

MODALITY	BENEFITS	FLAWS	INDICATION
CT	Fast acquisition speed. Indicated for many CNS emergencies. Comparatively low cost.	Ionizing radiation. Radiation risk compounded in the young. Poor resolution of parenchyma. Poor posterior fossa study.	Emergent imaging. Adequate for uncomplicated first seizure. Used in some epilepsy surgery planning. Evaluation of calcified lesions.
MRI	Good resolution. Flexible when using different sequences. No ionizing radiation. Safe for children.	Slow acquisition speed. Unable to scan patients with ferromagnetic implants. May require sedation in some patients. High cost. Limited availability.	Study of choice for evaluation of epilepsy. Study of choice for epilepsy surgery planning.



In the emergent evaluation of a new seizure, the 2007 AAN guidelines state that a CT scan be considered for adults presenting with a focal-onset seizure, an abnormal neurologic examination, or a predisposition for structural abnormalities (level B). The recommendation is similar for pediatric patients, though the consideration for imaging is only a level C recommendation. Emergent MRI had no significant evidence base at the time of those recommendations (14).

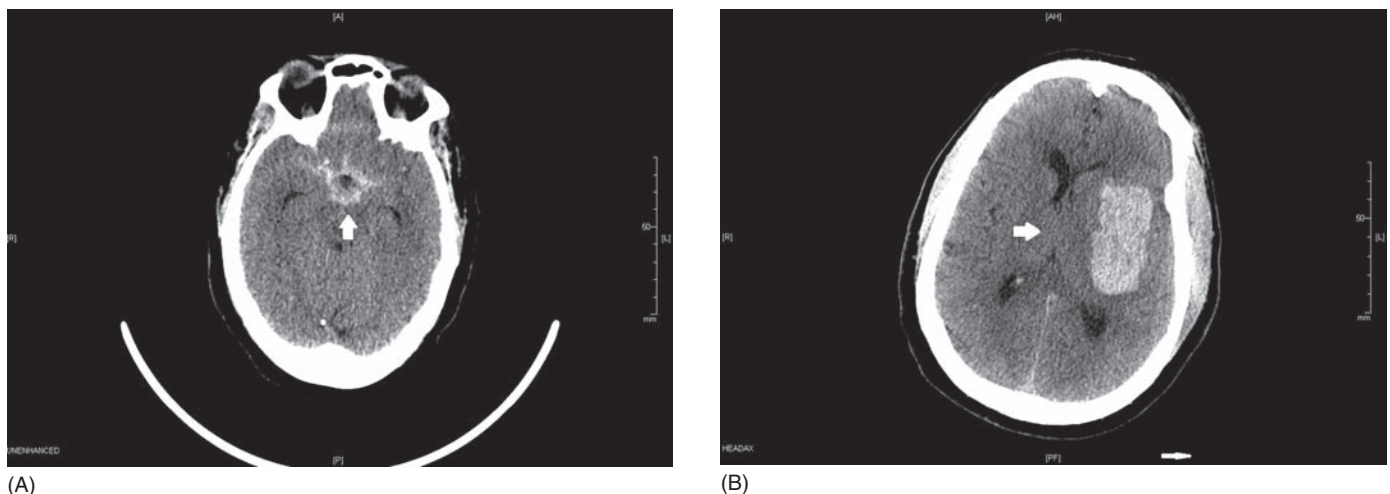
CT has practical advantages in the emergency setting. It is a fast study, making it easier to perform on an acutely ill patient than an MRI. It is already protocol in the evaluation of other acute neurological emergencies, such as stroke, and since seizure and stroke often occupy the same differential diagnosis, a noncontrast CT scan may be inevitable. On CT, many emergent seizure provocateurs are hyperdense, including acute intracranial bleeds—subdural, intraparenchymal, and subarachnoid hemorrhage—along with other gross abnormalities like large mass effect (Figure 20.1). Other lesions, such as smaller masses or inflammatory changes, may be better elucidated with the addition of a contrast agent, though this must be balanced with patient risk factors, such as renal impairment or a history of contrast allergy. Some findings such as small acute infarctions or posterior reversible encephalopathy syndrome may be best seen on MRI. Further imaging should follow if ongoing neurological findings are unexplained by a negative CT scan (14,16).

AAN guidelines for the evaluation of an apparent unprovoked seizure in adults recommend either a CT or an MRI as part of the workup for prognosis and management decisions (level B). Regardless of whether it is an emergent study or part of an outpatient workup, a patient should receive some form of structural neuroimaging after a first seizure (14).

The choice of CT or MRI is not specified in the guidelines, and is at the physician's preference. There is evidence that MRI has a higher yield for finding potentially etiologic abnormalities than CT; however, one recent comparison of CT versus MRI in the setting of an apparent unprovoked seizure showed that the yield of MRI over CT was minimal for patients with a normal neurologic examination and EEG (17). In an era of accountable care, and in the absence of explicit guideline recommendations, it is reasonable to reserve MRI for patients with clinical, electrographic, or CT abnormalities that raise the pretest probability of an etiologic anatomical lesion (14).

Imaging of the first unprovoked, nonfebrile seizure in the pediatric population is somewhat different. Given the risks of radiation, and the relatively lower probability of subsequent seizure recurrence, emergent imaging is only recommended in pediatric patients who have focal postictal abnormalities or a prolonged postictus; conversely, routine imaging should be considered in patients under 1 year of age, with unexplained cognitive impairment, an EEG that suggests an epileptiform activity outside of benign epilepsies of childhood, or evidence of a partial-onset seizure. The imaging modality of choice, emergently or as routine follow-up, is an MRI (18).

If a patient should develop epilepsy, either by suffering recurrent seizures or after a single seizure with features indicating a high risk of recurrence, CT is no longer sufficient. In their 1997 recommendations, the International League against Epilepsy (ILAE) explicitly states, "[MRI] is clearly the structural imaging modality of choice for investigating patients with epilepsy and is superior to radiographic CT in terms of both sensitivity and specificity for identification of small lesions and abnormalities of the cerebral cortex" (19). The guidelines specify MRI for focal-onset seizures,



**FIGURE 20.1** This is a collection of CT scans demonstrating acute hemorrhagic events. (A) Axial CT demonstrating a subarachnoid hemorrhage, originating in the right posterior communicating artery. Note the hyperdense blood casting the intrapeduncular cistern (large arrow). (B) Left lobar intracerebral hemorrhage with midline shift. Large arrow shows midline shift adjacent to the hyperdense bleed.

generalized seizures with onset before 1 year of age or in adulthood, seizures accompanied by fixed neurologic deficits, drug resistant epilepsy, or epilepsy with a loss of prior antiepileptic control.

In some patients, CT may be a necessary alternative to MRI. Patients with ferromagnetic implants, pacemakers, or implanted defibrillators are not MRI candidates. Likewise, some patients may not fit in the MRI or suffer from severe claustrophobia that can limit imaging. In underserved regions, MRI may not be available. Finally, in patients who have primary generalized epilepsy supported by EEG findings, an MRI may be deferred (19).

Where it is available and not contraindicated by medical conditions, MRI is considered the minimal essential standard of care for drug-resistant epilepsy or epilepsy accompanied by neurologic decline (13,19). Outside of this, CT is an alternative minimal standard, with the understanding that it can miss subtle findings, especially in the temporal lobe.

Given the preference for MRI, what sequences are necessary for evaluation of epilepsy? At minimum, an MRI should be obtained with 3D volume acquisition in T1- and T2-weighted sequences, with axial, coronal, and sagittal reconstructions. Multiplanar reconstructions can be useful, especially for evaluation of temporal lobe abnormalities or subtle cortical anomalies. FLAIR is useful and critical for identifying some lesions, such as mesial temporal sclerosis (MTS). The choice of other sequences can be institution- or physician-specific, and should be dictated by clinical concern. For example, if vascular malformations or focal microhemorrhages are suspected, susceptibility weighted imaging (SWI) or gradient echo (GRE) pulse sequences should be considered. The use of gadolinium contrast is not required per guideline recommendations, but it should be considered if a tumor or inflammatory process is suspected (9,13,19).

When a patient fails to respond to anticonvulsants, they may benefit from epilepsy surgery. Imaging in the epilepsy surgery candidate is an extension of imaging in the initial diagnosis of epilepsy: the resolution of anatomic detail is critical, so MRI is the mainstay. As with imaging for the initial workup of epilepsy, MRI is best performed with 3D volumetric acquisition, though tomographic acquisitions are adequate should they include axial, coronal, and sagittal sections; in practice, some institutions require an order to specify thin-cuts. Whether by acquisition or reconstruction, slice thickness should be as small as possible in the evaluation of epilepsy. Again, T1, T2, and FLAIR sequences are critical, at minimum in axial and coronal sections, though other sequences can be considered. Some experts also advocate for curvilinear reconstructions, especially when subtle neocortical dysplasia is suspected, though this is not available at all institutions. Contrast may be reserved for cases where tumor or inflammation is suspected (9,13).

CT has a limited role in the surgical epilepsy evaluation, usually in preparation for the surgery or to augment the MRI. In patients with calcified lesions, a CT may be able to help clarify the anatomical extent of calcification. CT angiography can be useful in operative planning for stereo-EEG surgery

to help surgeons avoid deep blood vessels during probe placement. CT may also be necessary to confirm and locate bone fiducials for stereotactic procedures.

Outside of the setting of a first seizure, initial epilepsy workup, and surgical evaluation, neuroimaging should be approached with some discretion. For patients with stable, or well-controlled epilepsy, and without findings concerning for malignancy, there is no particular need for repeated MRI or CT. Should there be a concern for malignancy or an inflammatory process, surveillance imaging at regular intervals can be performed until the clinician and patient are comfortable that the lesion is stable or it has progressed and requires intervention. Patients who lose control of previously drug-responsive epilepsy, patients who develop new seizure types, and patients who develop new cognitive or focal deficits in the setting of their seizures also warrant repeated imaging (9,13,19).

In sum, a CT is preferable in acute and unstable conditions, and when the differential includes structural neurologic emergencies; the MRI is preferable in situations of stability, where long-term planning and prognostication are in question. Imaging is best reserved for times of change: at the first seizure, at the initial diagnosis of epilepsy, when surgery is considered, in possible malignancy, and in periods of clinical decline.

## Common Etiologies

A number of common etiologies for focal and generalized epilepsy and their classic imaging findings are discussed further. This list is by no means exhaustive, but it is included to provide both examples of common diagnoses and to illustrate the imaging principles described earlier (Table 20.4).

### *Mesial Temporal Sclerosis*

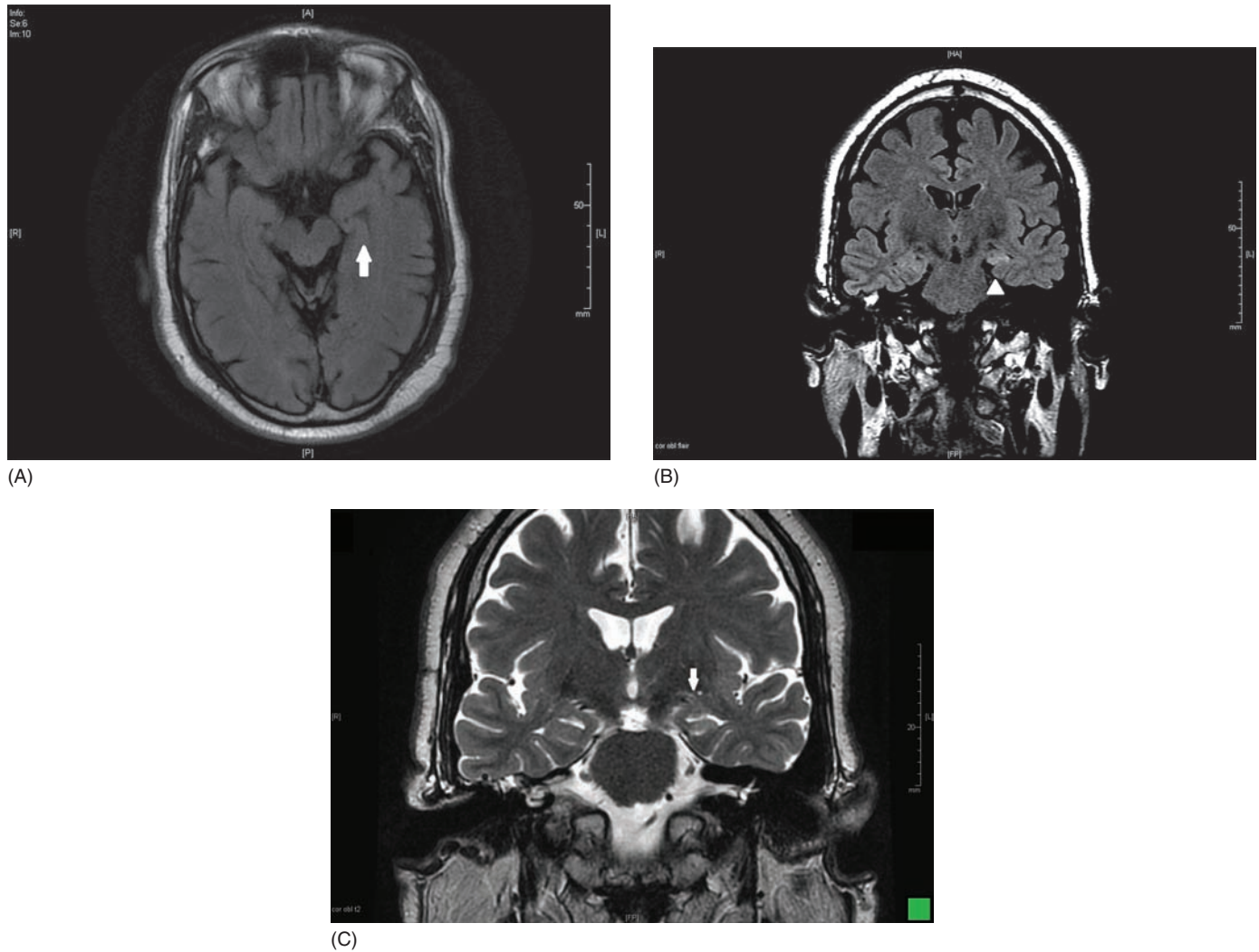
MTS is the most common cause of partial seizures in adults. It is best seen on coronal T2 or T2-FLAIR. MTS is associated with the triad of hippocampal atrophy, T2 signal hyperintensity, and a simplification of the hippocampal structure (Figure 20.2) (9).

The normal hippocampus is a mesial and somewhat caudal temporal lobe structure that appears as a laminated oval, or a flattened "C" shape in coronal cross section, and lies along a horizontal plane in the temporal lobe. Hippocampal atrophy is often manifested as a flattening of the cross section, often accompanied by a rotation or tilt to the residual hippocampal formation. This hippocampal atrophy is a product of scarring and a loss of cortical neurons. As a by-product of the cell loss and gliosis, the residual hippocampus develops T2 and FLAIR sequence hyperintensity, again, best seen in the coronal plane. The normal laminar structure of the hippocampus can also be simplified, leaving its cortex thinned. Hippocampal sclerosis is often accompanied by loss of volume in the whole temporal lobe, sometimes causing structural asymmetries seen in axial section in addition to the coronal plane. It is critical that T1, T2, and FLAIR sequences

TABLE 20.4 Summary of Neuroimaging Disease-Specific Imaging Findings

PATHOLOGY			COMMON FINDINGS
MTS			Triad of hippocampal atrophy, T2/FLAIR hyperintensity, and simplified structure.
Disorders of Cortical Organization	Cortical Dysplasia		Varies, depending on severity. Less severe lesions are subtle. More severe are T2 hyperintense, with dysmorphic cortex and transmantle sign.
	Heterotopia		Heterotopic nodules, or bands isointense to cortex regardless of pulse sequence.
	Lissencephaly		Smooth cortex with highly simplified or absent gyri.
	Polymicrogyria		Thickened cortex with numerous gyri, often with atypically bright white matter on T2 and T1 sequences with blurring of gray–white junction.
	Hemimegalencephaly		Hemispheric enlargement, always involving the cerebral hemisphere, but sometimes the cerebellum and brainstem as well. Can be associated with dysplasia and heterotopia.
Autoimmune Epilepsy			T2/FLAIR hyperintensity, frequently in the temporal lobes, occasionally with contrast enhancement.
Vascular Lesions	Strokes	Ischemic	Acutely, subtle or absent CT findings; MRI with hyperintensity on DWI and hypointensity on ADC sequences.
		Hemorrhagic	Very hyperdense on CT, dark on T2, and very dark on GRE/SWI from susceptibility artifact.
	Vascular Malformations	DVA	Subtle T1 and T2 findings, occasionally with a hyperintense blush on T2/FLAIR. Contrast can demonstrate a “caput medusae” pattern.
		Cavernoma	Susceptibility artifact on T2/FLAIR, and SWI/GRE. “Popcorn” shape.
		AVM	Flow voids are dark on T2, and gliosis and edema may be visible on T2/FLAIR. Bleeding will have susceptibility artifact on T2/FLAIR and SWI/GRE sequences. Bleeding is hyperintense on CT. Intravascular contrast studies are critical.
Tumors	Primary Neoplasms	Gliomas	Hypointense on T1, hyperintense on T2. Contrast enhance with high-grade malignancy.
		Oligodendrogliomas	Hypointense on T1, hyperintense on T2. Contrast enhance with high-grade malignancy.
		Meningiomas	Subtle, often isointense on T2 & T2. Dural tail can be present. Highly avid for contrast agents. Calcifications can be seen as hyperdensity on CT.
		DNETs & Gangliogliomas	Slightly hypointense on T1, heterogeneous hyperintensity on T2, sometimes with a cystic component. DNETs can contrast enhance.
	Metastatic Neoplasms		Cortically based T2 hyperintensity, often with marked edema also seen on T2/FLAIR sequences. Mass effect can be prominent. They can contrast enhance avidly.
	Hamartomas		Masses are isointense at the cortex and T2/FLAIR hyperintense in the subcortical white matter. They occasionally enhance. Isointense intraventricular masses. White matter cysts.





**FIGURE 20.2** Mesial temporal sclerosis. (A) Axial FLAIR—the large white arrow demonstrates overall temporal lobe volume loss and enlargement of the CSF spaces. (B) Coronal FLAIR—note the decreased size of the left hippocampus and the increased FLAIR hyperintensity. (C) Coronal T2—there is a simplification and rotation of the hippocampus (small arrow).

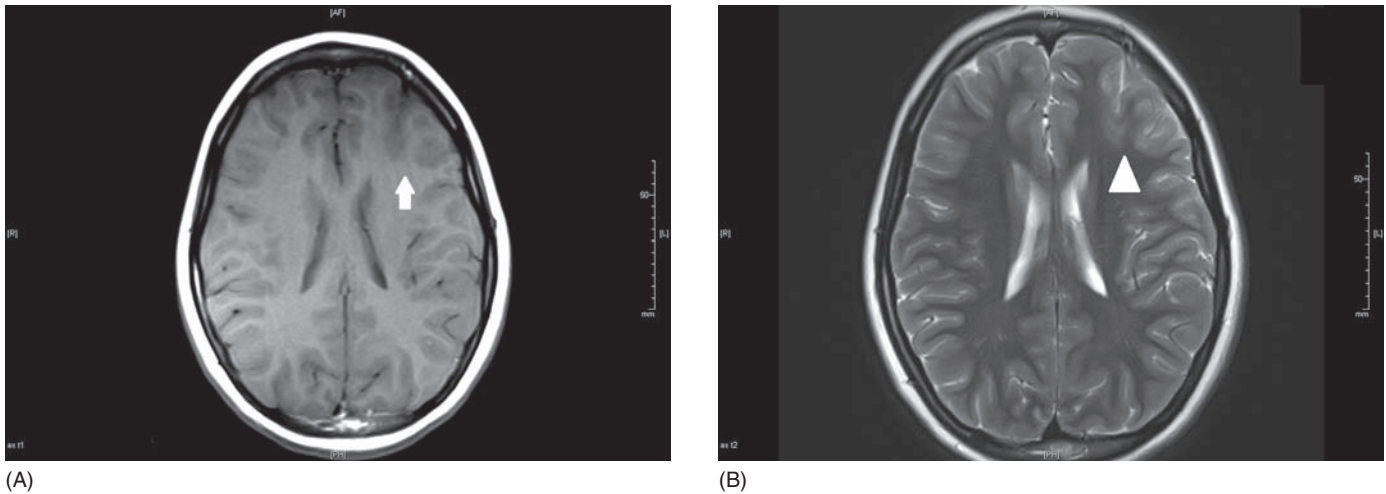
in the coronal section be ordered with as thin cuts as are available, should MTS be in the differential (9).

### *Disorders of Cortical Organization*

A broad category of congenital developmental defects involving the proliferation, migration, and organization of the cerebral cortex can all lead to epilepsy. The imaging findings for these range from subtle cortical abnormalities that cannot be resolved on common clinical MRI scans to gross abnormalities large enough to be detected by fetal ultrasound. Several of these common abnormalities seen in epilepsy are reviewed later.

**Cortical Dysplasias.** Cortical dysplasias are a heterogeneous group of cortical proliferation abnormalities that are often highly epileptogenic, and frequently result in seizures that are refractory to medication. They range in a spectrum of severity,

from subtle derangements in cortical lamination or neuron orientation to dysmorphic neurons and balloon cells. The MRI findings of cortical dysplasia lie along a similar spectrum of severity. MRI findings for lamination or cellular organization defects can include subtle cortical thickening or thinning. There may be blurring of the gray–white matter junction. Sulcation may be excessively deep or shallow. Alternatively, MRI may not have the resolution to identify such subtle abnormalities. As the cellular structure becomes more aberrant, MRI is more likely to demonstrate T2 hyperintensity, and cortical thickening can be more distinct, though subtle findings noted previously are not uncommon. In severe dysplasias with balloon cells, T2 signal hyperintensity in the subcortical white matter regions can be prominent. Gyri and sulci can be grossly abnormal, and thickening tends to be more overt than in lesser dysplasias. Transmantle sign, a fading white matter lesion reaching from the dysmorphic cortex to the ventricle, can also be seen (Figures 20.3, 20.4) (9,20,21).

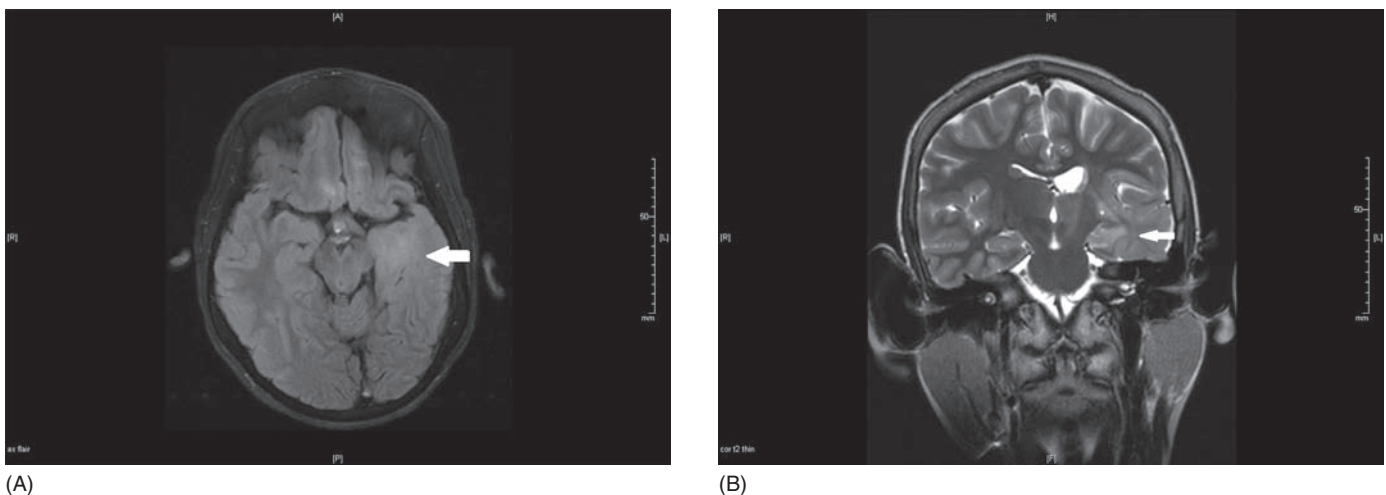


**FIGURE 20.3** This is a left frontal cortical dysplasia. (A) Axial T1 demonstrating a deep sulcus with an indistinct gray–white matter junction (arrow). (B) Axial T2, with cortical T2 hyperintensity extending into the white matter (arrow head).

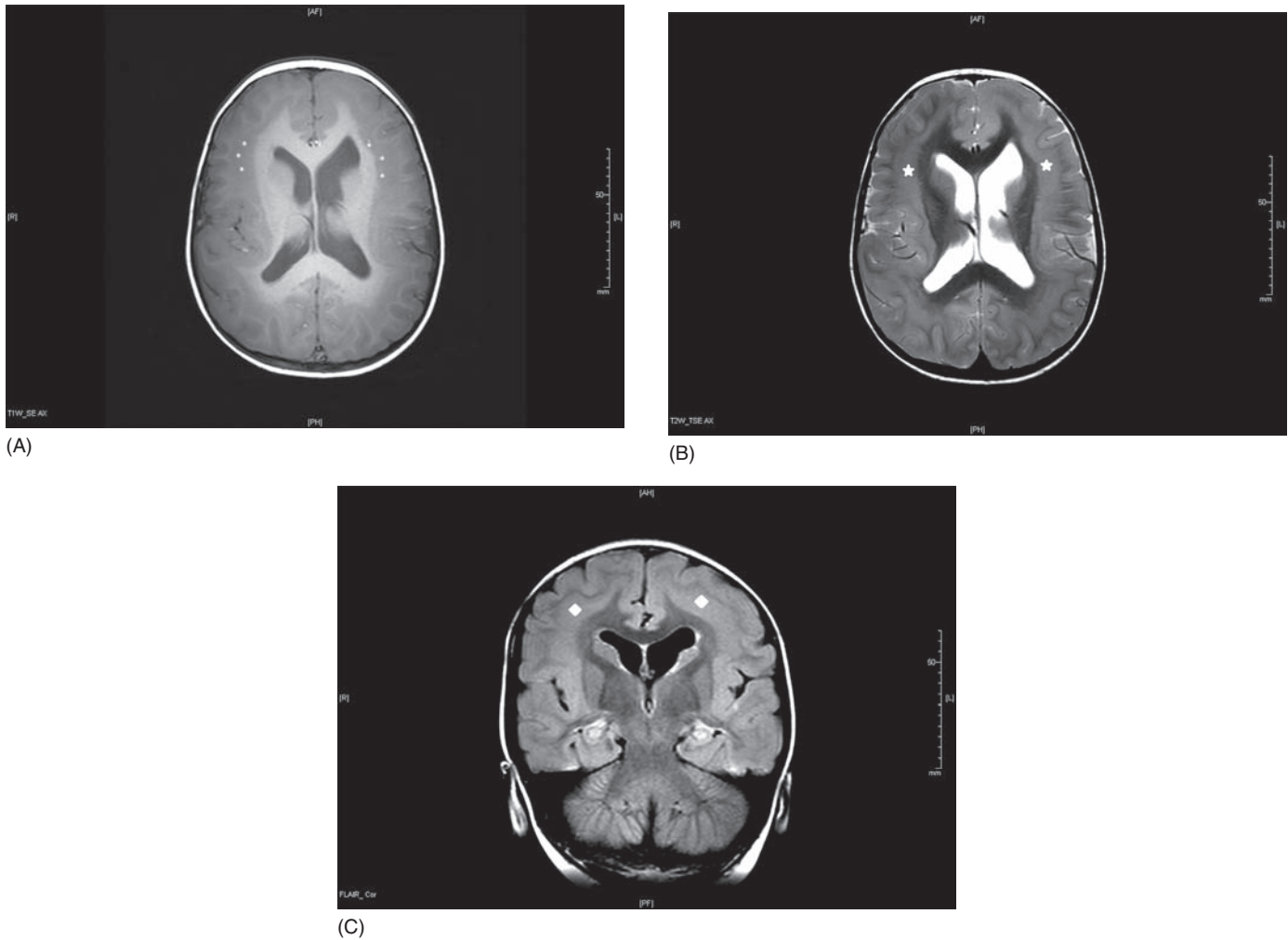
**Heterotopias.** Gray matter heterotopias are abnormalities of neuronal migration. Gray matter heterotopias can be broken down into subependymal, subcortical, or band heterotopias, depending on where the migration arrest occurred. Because the heterotopias consist of misplaced gray matter, they will be of the same signal intensity as normal cortex on any given MRI sequence. MRI findings may be subtle, but heterotopias can be identified as rest of tissue, isointense to cortex, either projecting into the ventricle (subependymal or periventricular), or lying in a field of white matter (band or subcortical) (Figure 20.5). Shape is also an important consideration: heterotopia can be described as nodular, curvilinear, or band. Band heterotopias can be particularly striking, giving the appearance of a “double cortex.”

Heterotopias are often accompanied by cortical dysplasia, with similar abnormalities as described earlier (21).

**Lissencephaly.** Lissencephaly, literally meaning “smooth brain,” is a group of organizational disorders characterized by an absence of gyri and sulci, leaving a very simplified cortical surface. Attributable to several different genetic abnormalities, lissencephalies can be either errors of fundamental neuron proliferation (microlissencephaly or a smooth brain coupled by severe microcephaly), or a defect of migration (classical lissencephaly, Figure 20.6). Another variant, cobblestone lissencephaly, is an overmigration defect, frequently seen in congenital muscular dystrophies.



**FIGURE 20.4** Left mesial temporal cortical dysplasia. (A) Axial T1 showing an enlargement of the mesial temporal structures with loss of sulci and no definite gray–white matter border (arrow). (B) Coronal T2 showing asymmetric enlargement of the left lateral ventricle, white matter hyperintensity in the mesial temporal white matter (thin arrow), with transmantle sign (asterisk).



**FIGURE 20.5** Band heterotopia. (A) Axial T1 image with the heterotopia represented by bilateral strips of tissue isointense to the gray matter (asterisks). It is rimmed proximally and distally with white-matter hyperintensity, thinner in the subcortical regions, thicker in the periventricular regions. (B) Axial T2 sequence of the same cross section. Note how the heterotopia remains isointense to cortex, despite the changes in signal intensity from the T1 sequence (stars). (C) FLAIR sequence showing the same band heterotopia in coronal section (diamonds).

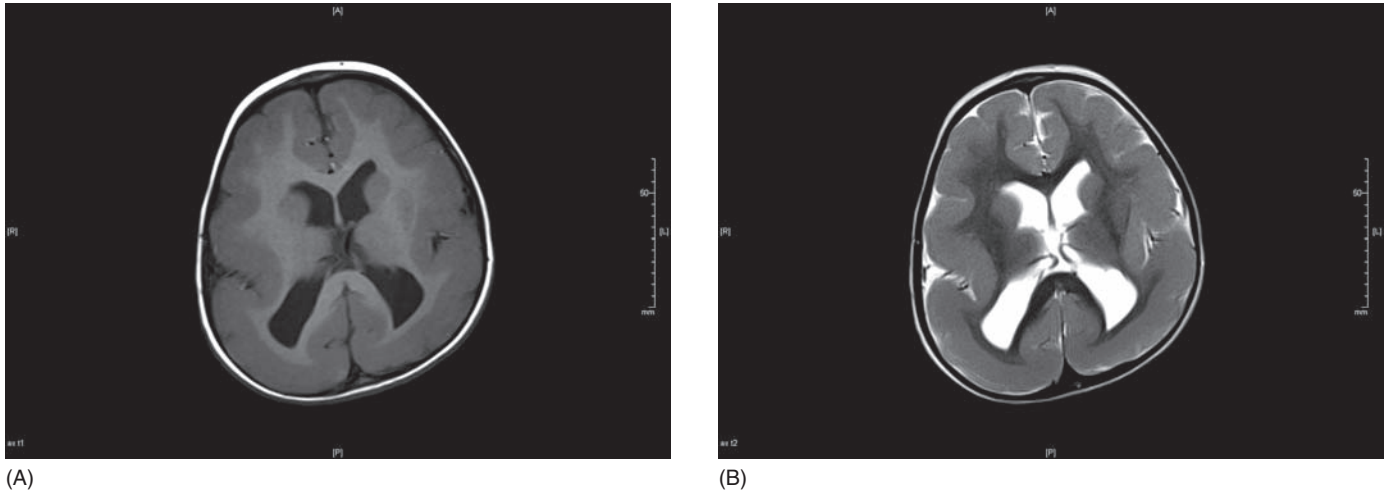
Any of these causes lead to varying degrees of developmental disability and epilepsy (21).

**Microlissencephaly** appears as a globally small brain with reduced cortical folding, ranging from areas of mildly reduced sulcation to a complete agyral cortex. Best seen on MRI, the cortex will appear thickened, greater than three millimeters. Classical lissencephaly also appears with flattening of the cortical surface, ranging from complete agyria to mild temporal and frontal gyrus formation. Microscopically, classical lissencephaly has only a four-layer cortex, though on MRI imaging it will also appear thicker. The gray–white matter junction is also smoothed and simplified, and there can be regions of T2 hyperintensity in the white matter. Cobblestone lissencephaly is similar, though the surface of the cortex has coarse blocky character. Depending on the severity of the genetic abnormality, the white matter will have varying

degrees of poor migration, and the posterior fossa will show some degree of cerebellar and brainstem deformity (21).

**Polymicrogyria.** Lissencephaly can be confused with polymicrogyria, a disorder of cortical organization. In polymicrogyria, the six-layer cortical structure is preserved, but the gyri are smaller, finer, and packed together. On an MRI, the cortex appears slightly thicker than normal, and the normal gyral pattern will be shallower and less distinct. It comes in two patterns. Type I is an infantile pattern with very fine frontal gyri. White matter T2 signal can also be brighter. Type II is seen in older children, after 18 months, and is coarser and more diffuse than the frontally predominant type I (Figure 20.7). T1 sequences will have poor gray–white differentiation (21).





**FIGURE 20.6** Classical lissencephaly. (A) Axial T1 demonstrating a patient with a normal head circumference for age and height, demonstrating global simplification of gyri, along with a marked thickening of the cortex. (B) The same cross section by T2 pulse sequence.

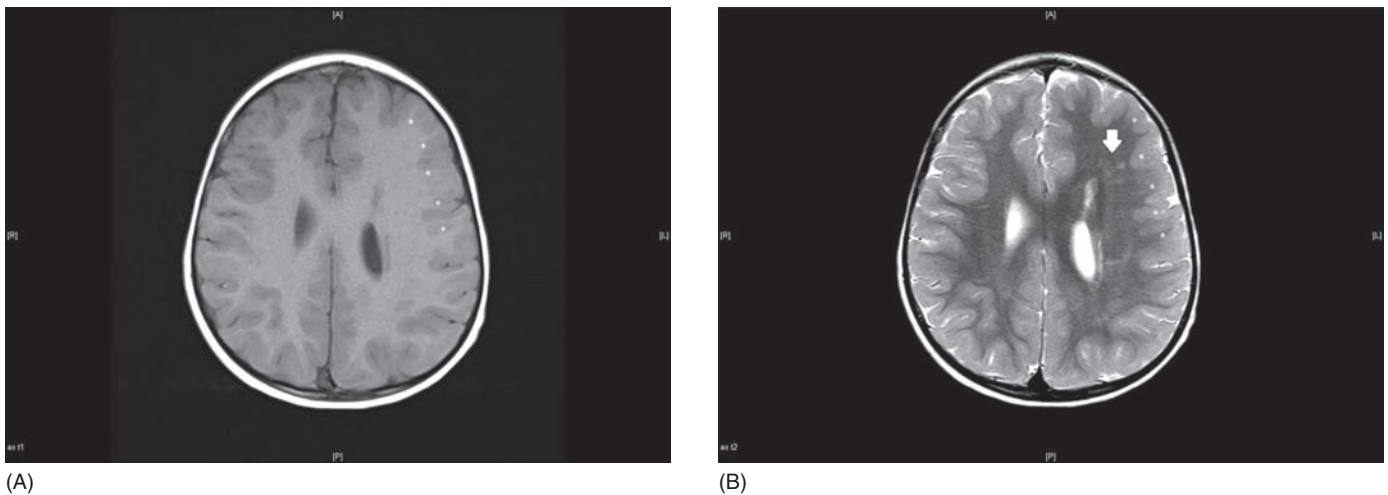
*Hemimegalencephaly.* Hemimegalencephaly, a syndrome of cerebral hemi-hypertrophy, is a rare cause of partial epilepsy, though easily recognized due to its characteristic imaging findings. While distinct from disorders of cortical organization, it is frequently accompanied by dysplasias and heterotopias. However, the critical feature is an enlargement of the entirety of one cerebral hemisphere, and often the ipsilateral cerebellum and brainstem (Figure 20.8).

Hemimegalencephaly is best evaluated by MRI, which, in addition to hemispheric enlargement, can also demonstrate some of the features of cortical disorganization described earlier. On T2, enlarged vascular flow-voids may be seen, along with an enlarged ipsilateral lateral ventricle. Cerebellar enlargement can be seen in conjunction with

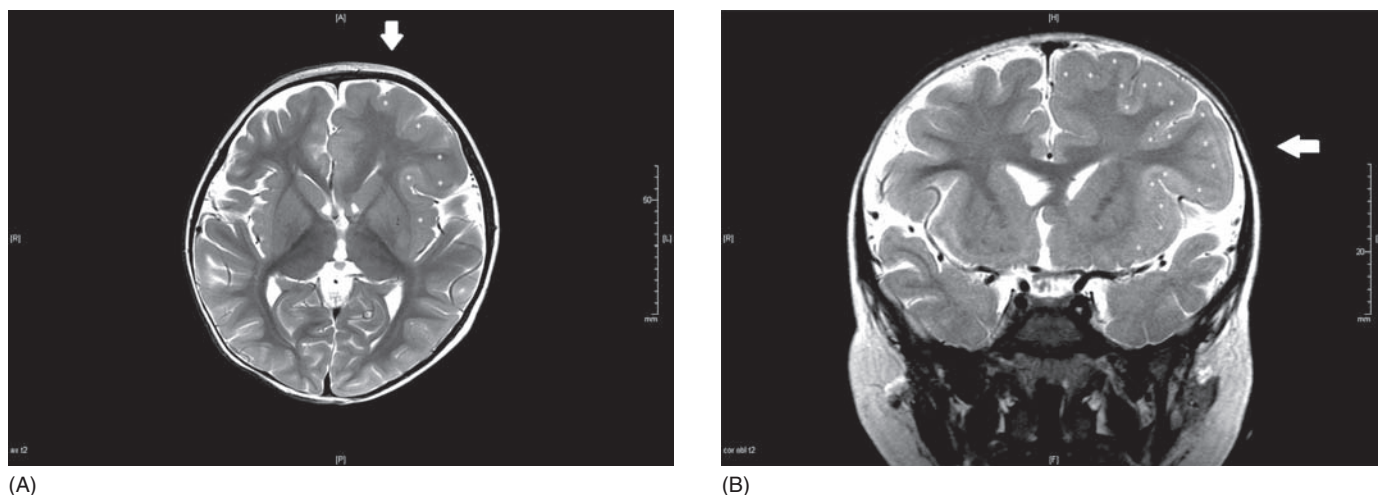
abnormal cerebellar folia patterns, and the midbrain and pons may show hemi-hypertrophy as well (21).

### *Autoimmune Epilepsy*

Autoimmune epilepsy has become a significant concern in the past decade. While uncommon, autoimmune epilepsy can be rapid in onset, tends to be refractory to treatment, and can be accompanied by debilitating cognitive, psychiatric, and focal neurological deficits. In one case series by Quek et al. of 32 patients with epilepsy attributed to an autoimmune inflammatory process, 53% had imaging abnormalities on MRI at the time of diagnosis, and 63% by the end of the study. Imaging findings were diverse, but a full



**FIGURE 20.7** Polymicrogyria. (A) Axial T1 sequence showing left frontal polymicrogyria, with abundant coarse gyri formed by shallow sulci (asterisks). (B) T2 sequence of the same axial cut—note the heterotopia accompanying the polymicrogyria (arrow).



**FIGURE 20.8** Hemimegalencephaly. (A) Axial T2 sequence demonstrating a grossly enlarged left hemisphere (arrow), along with thickened, indistinct cortex with enlarged gyri, consistent with an accompanying cortical dysplasia (asterisks). (B) T2 sequence demonstrating the same patient in coronal section, with the left hemisphere and cortical dysplasia similarly marked.

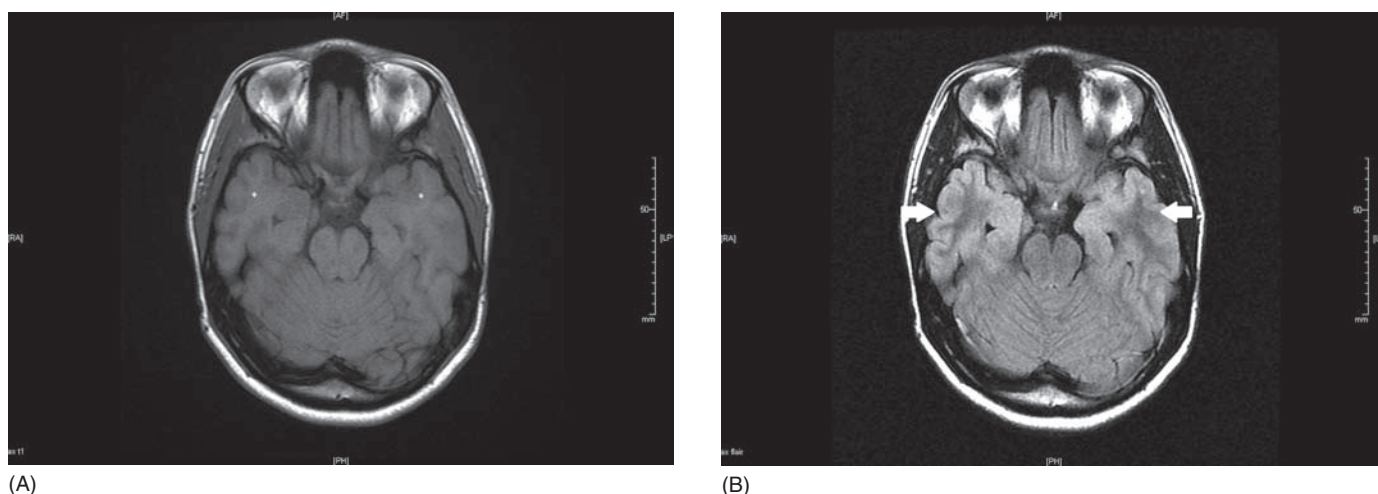
53% showed mesial temporal swelling with T2 hyperintensity, and another 19% had edema elsewhere in the temporal lobes. While only 19 patients received gadolinium contrast during MRIs, one-third had contrast enhancement. Four patients had findings consistent with mesial temporal sclerosis. While the absence of abnormalities on MRI should not rule out a diagnosis of autoimmune epilepsy, the presence of swelling, T2 hyperintensity, and contrast enhancement in the temporal lobes can raise the index of suspicion for an autoimmune process (Figure 20.9) (22).

A discussion of imaging in autoimmune epilepsy would not be complete without mentioning Rasmussen's encephalitis, a focal inflammatory process felt to be T-cell mediated, and known for causing epilepsy partialis continua. The

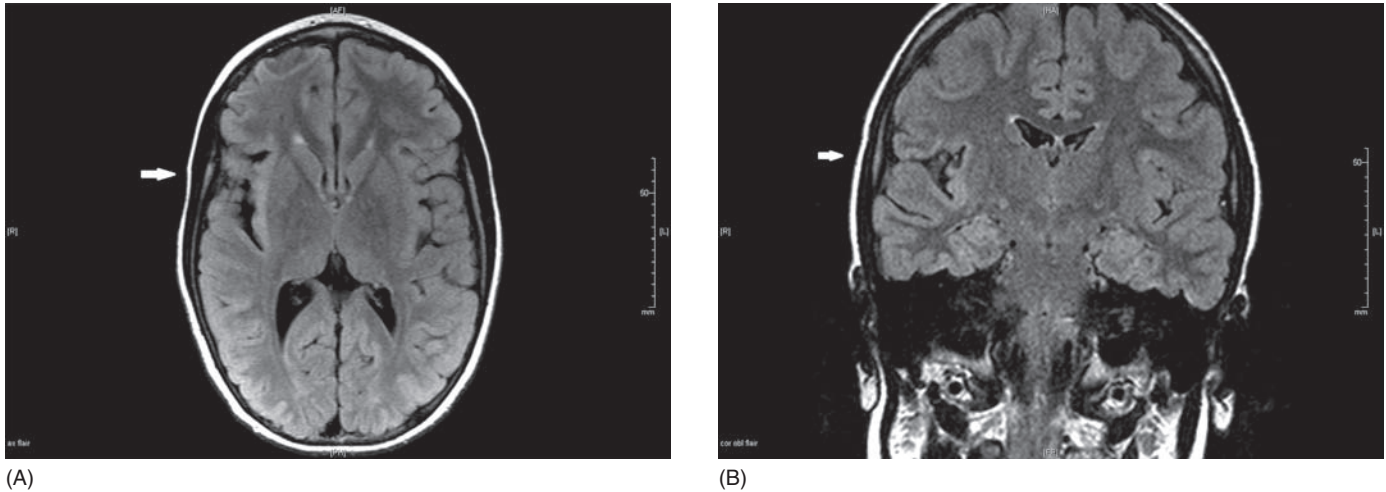
hallmark-imaging finding is a hemi-atrophy, beginning in the region of the insula and expanding throughout the remainder of the hemisphere. Best seen on MRI on T2 and FLAIR sequences, the atrophy is often accompanied by hyperintensity in the region of atrophy. In patients, usually young children, presenting with refractory highly focal motor seizures, imaging should be examined closely for opercular asymmetry and T2 signal change (Figure 20.10).

### *Vascular Lesions*

Brain vascular lesions are common causes of acquired epilepsy. This is a varied collection of pathologies, and their discussion will be simplified by breaking them down into strokes and vascular malformations.



**FIGURE 20.9** Autoimmune encephalitis causing epilepsy. (A) There is a subtle loss of distinction of the gray-white matter junction in the temporal lobes on a T1 axial sequence (asterisks). (B) Axial FLAIR sequence highlights the abnormality, demonstrating bilateral temporal cortical hyperintensity, with the mesial temporal lobes particularly hyperintense.



**FIGURE 20.10** Rasmussen's encephalitis. (A) Axial FLAIR demonstrating insular atrophy and a subtle hyperintensity of the cortex (arrow). (B) FLAIR sequence, with a coronal view of the same patient. Note the opercular atrophy is more apparent in this cross section (small arrow).

**Strokes.** Stroke is a general term for an acute vascular insult, either ischemic or hemorrhagic in nature. Ischemic events are more common, and can be a product of occlusions of either the arterial or venous circulation. Both arterial and venous infarctions can cause acute seizures and chronic epilepsies. In the acute and emergent setting, CT is the study of choice, though it frequently does not show the abnormality. However, CT rules out the presence of hemorrhage, and can identify hyperdensities that can represent either large artery or large vein thrombosis. Other hyperacute findings on CT are loss of gray–white differentiation or blurring of the deep nuclei. MRI can demonstrate restricted diffusion—appearing bright on DWI and dark on ADC-map sequences, and T2 signal may be hyperintense as the stroke evolves. MRI is superior to CT in sensitivity and specificity for stroke, though in the emergent setting, CT may be preferable, especially if thrombolysis is under consideration. After the acute phase, especially when beyond the treatment time for thrombolysis, MRI becomes preferable to CT. There are a series of changes that appear on MRI in the acute, subacute, and chronic phases of infarction and recovery, though this is beyond the scope of this chapter.

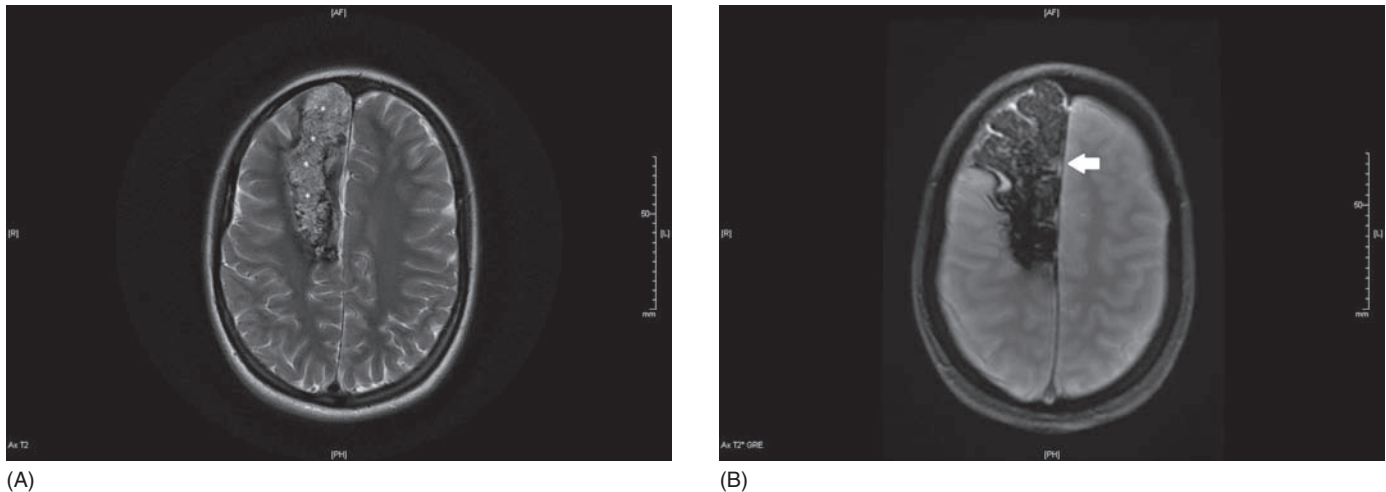
Hemorrhages can be subarachnoid, intraparenchymal, or subdural. CT without contrast is the imaging study of choice for acute hemorrhagic changes (Figure 20.1). T2 and FLAIR MRI sequences can also be used to identify acute hemorrhages of each of these types. GRE or SWI sequences, exquisitely sensitive to small amounts of deoxyhemoglobin, can be used to assess for microhemorrhage as well. As blood ages, it can be more difficult to appreciate on CT scan, though it can cause long-standing changes on MRI with characteristic patterns of evolution.

**Vascular Malformations.** The most common vascular malformations are developmental venous abnormalities (DVA). They consist of dilated draining veins, surrounded by normal brain tissue. They can be associated with seizures, assumed to be related to historic bleeds or oozing. On T1 and T2 sequences, DVAs may be hard to see, though T2 can demonstrate a blush. CT has some utility, as a thrombosed DVA will appear hyperdense. Intravascular contrast on any modality can create a “caput medusa” picture of a central region of enhancement with a draining vessel.

The second most common abnormality is the cavernous hemangioma (also cavernous angioma, or cavernoma), dilated collections of endothelial caverns. They do not consist of true blood vessels, and they lie in a bed of abnormal parenchyma. CT will generally miss the actual lesion, but if calcified, it will demonstrate the hyperdense calcifications. MRI is quite sensitive, as cavernomas tend to leak blood overtime, and there is a dark susceptibility artifact ring on T2 and FLAIR sequences, and can be well demarcated with SWI or GRE sequencing, often with a lumpy or “popcorn” shape (Figure 20.11).

Arteriovenous malformations (AVMs) are a collection of lesions consisting of abnormal arterioles connecting with abnormal venules, without intervening capillary beds. The exposure of the venous circulation to arterial pressure is unstable, and thus AVMs have a high rate of bleeding. If acutely ruptured, CT, T2 MRI, and SWI or GRE sequences are adequate tools for evaluation. In the absence of a bleed, they may not be evident on CT, though with contrast enhancement the blood vessels show up readily and can allow for surgical planning if necessary. Chronically, and in the absence of bleeding, CT angiography is an option for characterizing the vascular component, which appears as a





**FIGURE 20.11** Cavernous hemangioma. (A) Axial T2 sequence demonstrating a large cavernoma, apparent as a mottled, “popcorn-texture,” mixture of hyperintense and hypointense structures, surrounded by a very-hypointense ring of susceptibility artifact from the accumulated blood products (asterisks). (B) The same axial section by GRE sequence—note how GRE intensifies the hypointensity of the blood in and around the lesion (arrow).

knot of dilated vessels, though it offers little to characterize the surrounding parenchyma. MRI can resolve the blood vessels by demonstrating flow void on T2, appearing as strongly hypointense vessels. The presence of adjacent gliosis and edema, especially in residual cortical regions, will show as a bright region on T2 (23).

### *Tumors and Hamartomas*

Mass lesions of either neoplastic or hamartomatous origin can be highly epileptogenic. While these lesions often present with epilepsy, they are not a common cause of epilepsy. Nonetheless, they are readily identified with anatomical neuroimaging studies and will be reviewed briefly.

**Primary Neoplasms.** A detailed discussion of neuroimaging in CNS neoplasms is beyond the scope of this chapter, but since tumors can cause epilepsy, general principles will be discussed.

As with disorders of cortical migration, MRI is the primary tool for anatomic imaging of tumors. CT does not offer adequate discrimination of parenchymal tissue variations, particularly in the posterior fossa, and while postcontrast CT may detect enhancement in high-grade malignancies, it tends to miss low-grade neoplasms. MRI is favored, and T2 or FLAIR pulse sequences, along with postcontrast scans are the most useful imaging approaches.

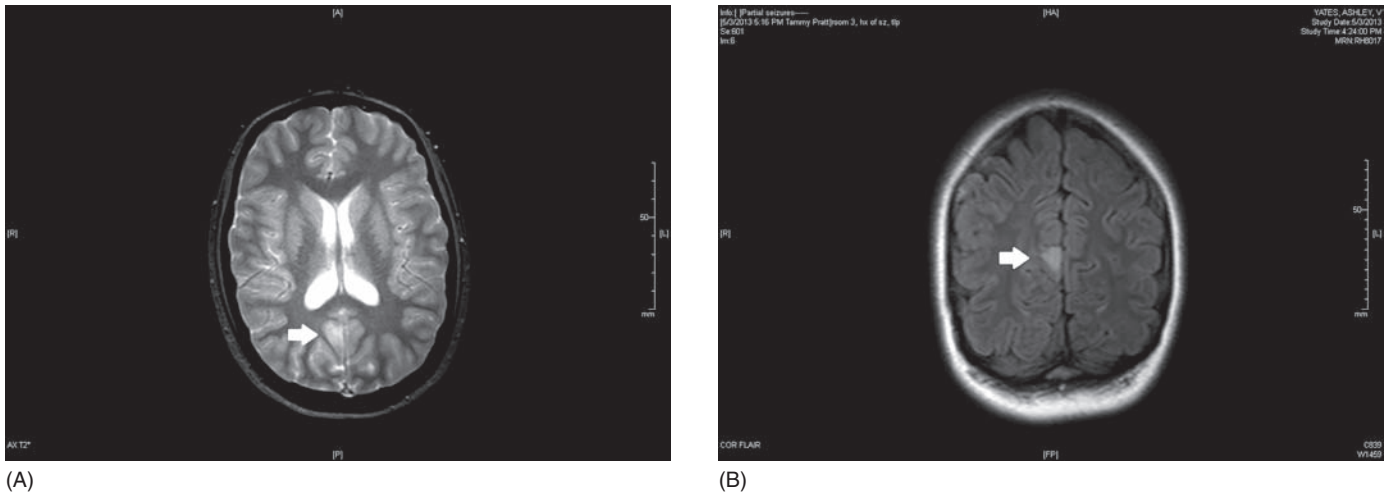
Gliomas, in general, tend to be hypointense on T1 because of decreasing lipid density and hyperintense on T2, because of the increase in edema. The greater the edema, the more prominent it will appear on T2, and likewise, greater tissue distortion provides structural clues to mass location (Figure 20.12). High-grade glial tumors can demonstrate

neovascularization and central necrosis and are frequently identified by contrast, classically with a ring-enhancing pattern. The malignancies may appear discrete, especially when contrast enhanced, but are very invasive, and T2 signal changes can be widely distributed. Oligodendrogliomas and oligoastrocytomas, too, are hyperintense on T2, and can have cystic regions that appear hypointense when seen in FLAIR sequences (Figure 20.13).

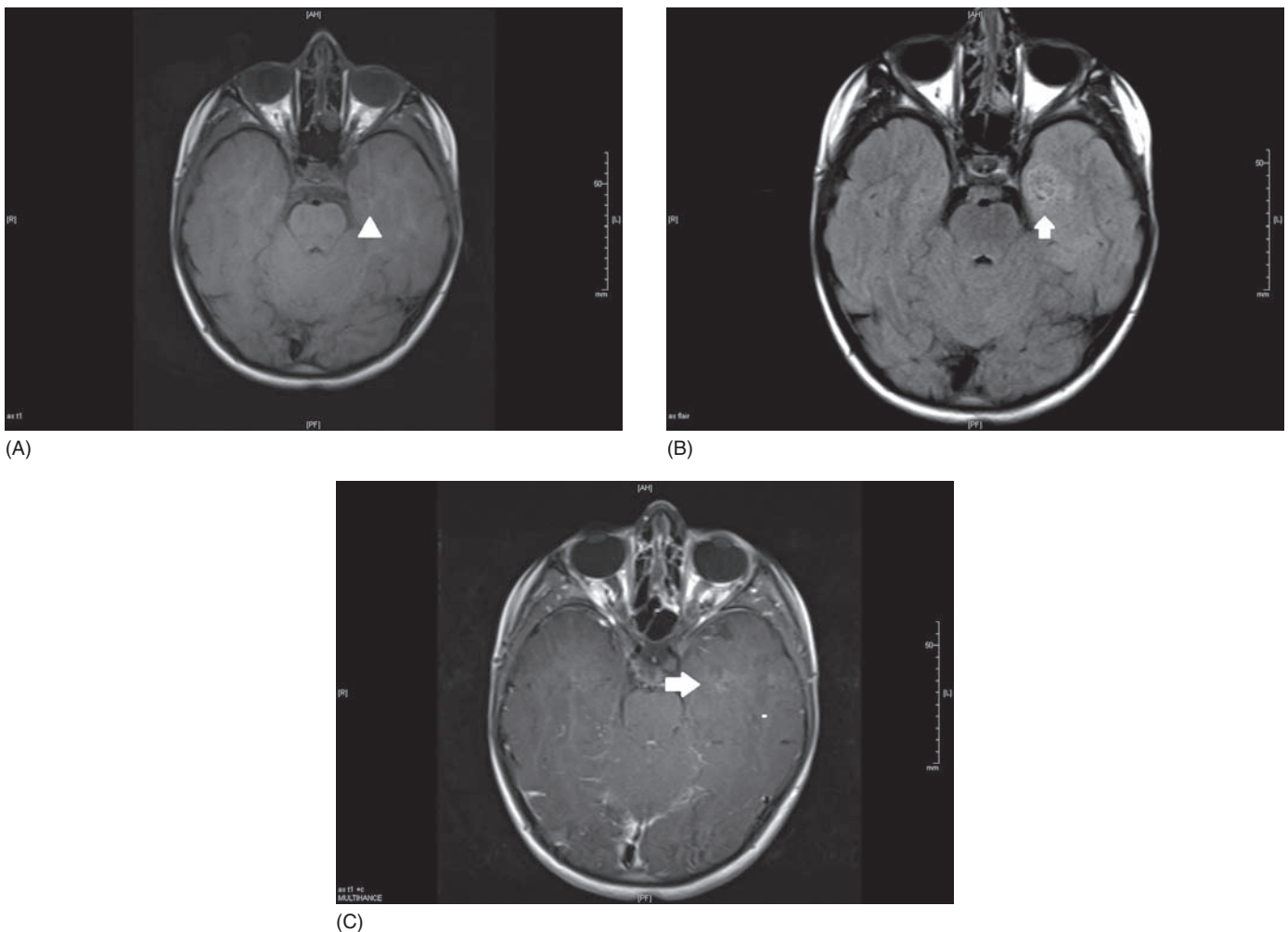
Meningiomas are also epileptogenic. They are extra axial masses, emerging from the skull with a characteristic convex appearance called a “dural tail.” They tend toward isointensity on T1 and T2, unless they cause edema, but they are strongly contrast enhancing (Figure 20.14). Because they can calcify, they may be detected on CT, though MRI is still favored (24).

Dysembryoplastic neuroepithelial tumors (DNETs) and gangliogliomas are also highly epileptogenic masses, made of mixed glial and neuronal elements. They are slow growing and likely products of maldevelopment of neuronal structures. DNETs favor the temporal and frontal lobes. Findings on MRI tend toward T1 hypointensity and T2 and FLAIR sequence hyperintensity. Edema can be present and visible on T2 and FLAIR, though mass effect is negligible. The hyperintensity is not uniform within the lesion. Contrast enhancement is variable, from nonenhancing to highly avid lesions (Figure 20.15). Gangliogliomas appear similarly, with hypointensity on T1 and hyperintensity on T2 and FLAIR sequences, though they are more frequently cystic and heterogeneous than DNETs. Contrast enhancement is less apparent (25).

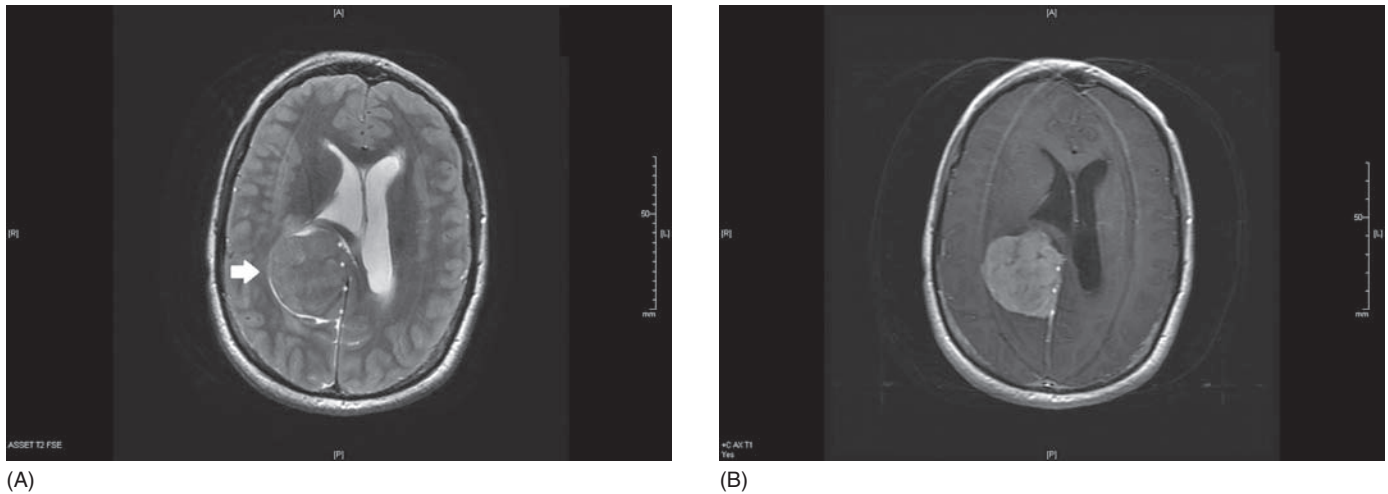
**Metastatic Neoplasms.** Metastases are more common than primary malignancies of the CNS and can also be



**FIGURE 20.12** Astrocytoma. (A). Axial T2 sequence showing an asymmetric hyperintensity in the mesial occipital region (arrow). (B) FLAIR showing the same lesion in coronal section, more apparent with the attenuation of the surrounding CSF (arrow).



**FIGURE 20.13** Oligoastrocytoma. (A) Axial T1 demonstrating a mesial temporal enlargement with a subtle hypodensity (arrow head). (B) The same axial section by FLAIR sequence, demonstrating a mildly hyperintense mass, with small hypointense cystic components (arrow). (C) T1 postcontrast image of the same section, demonstrating mild enhancement of the lesion (large arrow).

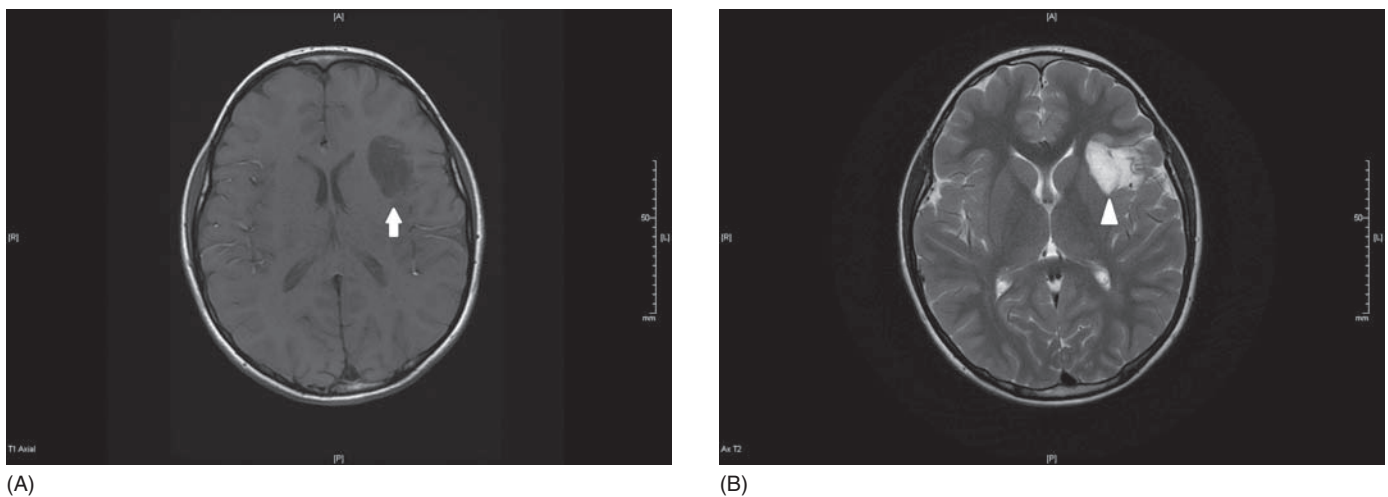


**FIGURE 20.14** Meningioma. (A) This axial T2 image demonstrates an isointense mass emerging directly from the falx cerebri (mass marked by arrow, dura by asterisks). There is subtle hyperintense edema surrounding the lateral aspect of the meningioma. (B) Axial T1 postcontrast image of the same patient, demonstrating bright homogeneous enhancement, with the attachment at the falx cerebri more apparent (asterisks).

epileptogenic. They tend to be cortically based and favor the anterior fossa. Much like primary malignancies, brain metastases are best seen by MRI, though CT can identify tumors in some situations. On CT, malignancies can appear iso-, hyper-, or hypo-dense, depending on the tissue of origin and the degree of vasogenic edema. Notably, melanomas are strongly hyperdense—almost appearing as if contrast enhancing. On MRI, metastases behave similarly to primary malignancies and tend toward iso- or hypointensity on T1 and hyperintensity on T2, with greater edema associated with greater signal prolongation. They tend to show facilitated diffusion and are hyperintense on ADC-map sequences.

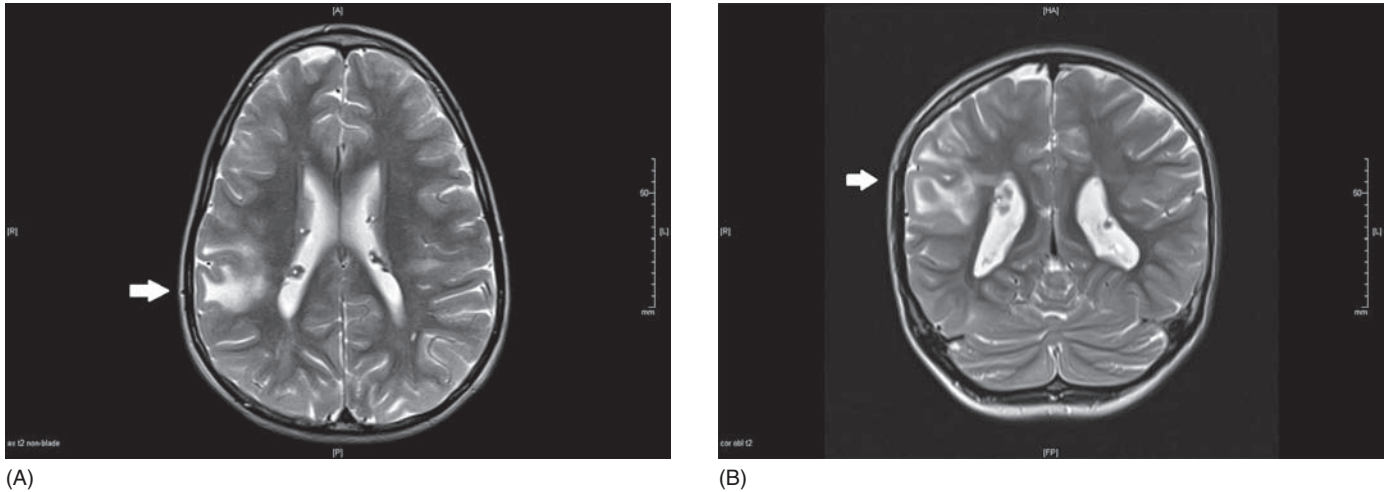
However, lesions with limited edema can be difficult to see as they are less T2 hyperintense. Metastases tend to strongly enhance with gadolinium contrast.

**Hamartomas.** Tuberous sclerosis is the prototypical disease of CNS hamartomas. It is an autosomal dominant disorder that leads to the upstream dysregulation of the mammalian target of rapamycin (mTOR), leading to disorganized and hyperproliferative tissues in multiple organ systems. CNS manifestations include cortical tubers—a form of hamartoma, along with subependymal nodules and subependymal giant cell astrocytomas (SEGAs).



**FIGURE 20.15** DNET. (A) Axial T1 image demonstrating a left frontal hypointensity (arrow). (B) The same patient with an axial T2 image demonstrating prominent heterogeneous hyperintensity reaching to the cortex (arrow head).





**FIGURE 20.16** Tuberous sclerosis. (A) Axial T2 image demonstrating a tuber (arrow) with a cortical component isointense to the surrounding normal cortex, and a hyperintense subcortical component extending deep into the white matter. The white-matter-isointense subependymal nodules project into the lateral ventricles, and are silhouetted against the hyperintense CSF (asterisks). (B) Coronal T2 image of the same patient, with the tuber and subependymal nodules (similarly marked).

Cortical tubers appear as a mass with a rim isointense to cortex and a T2 hyperintense subcortical component. This is because the cellularity of the cortical component of the hamartoma resembles the surrounding cortex, but the subcortical component has higher water content. As a consequence, they may be difficult to identify in infants, due to the globally poor myelination masking the tubers T2 signal. They can occasionally contrast enhance, though this is not uniform and should not rule in or out the diagnosis. Subependymal nodules and SEGAs tend to be isodense to periventricular tissues on T1 and T2. Sometimes they calcify, so they may be visible as a hyperdensity on CT, but their characteristic feature is that they are silhouetted against the lateral ventricles (Figure 20.16). SEGAs classically appear adjacent to the foramen of Monro, and can be associated with an obstructive hydrocephalus (9,26).

In the course of a century, neuroimaging has grown from painful and poor-resolution pneumoencephalograms to high-resolution spiral CTs and MRIs. CT and MRI use fundamentally different physical principles to acquire anatomic images, and this gives each modality unique merits and flaws. CTs are fast, ubiquitous, and relatively inexpensive, making them excellent emergent screening studies. However, they offer limited resolution and carry a risk of radiation exposure. MRIs are slower, are difficult to perform on decompensated patients, and are not available in all jurisdictions. They are also expensive to use and maintain, and this leads to increase costs for the patient. However, they can provide exquisite detail and can differentiate subtly dissimilar tissues, such as gray and white matter structures. They also emit no radiation, and are relatively safe to perform serially. CT scans are

recommended for the emergent evaluation of first seizures, and there is evidence that, for selected patients, MRI offers little incremental benefit for the workup of a first-time unprovoked seizure. However, guidelines are firm that MRI is the mainstay of the workup of formally diagnosed epilepsy and refractory epilepsy. MRI can be tremendously useful for identifying both subtle and blatant structural abnormalities, such as MTS, cortical dysplasia, gray matter heterotopias, and inflammatory processes.

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# Functional Neuroimaging

*Jorge Oldan, Terence Wong, and Jeffrey Petrella*

Functional imaging, referring here to nuclear techniques such as PET and SPECT, as well as functional magnetic resonance imaging (fMRI), is primarily useful in the surgical treatment of epilepsy. PET and SPECT are primarily used to localize potential candidates for resection of an epileptogenic focus, whereas fMRI is principally used to map crucial areas and aid in surgical planning.

While 70% of epilepsy patients can be treated medically, others may require surgical resection of the epileptogenic focus. Surgery is successful (defined as resolution of seizures over a period of 2 years after resection) in 60% to 90% of cases of temporal lobe epilepsy (TLE) and 22% to 65% of cases of extratemporal epilepsy (1). Usually, MRI is the favored modality for detecting structural abnormalities such as hippocampal or mesial temporal sclerosis (where patients also have the best postsurgical prognosis) (1). However, if MRI is normal (as in 20% to 25% of cases (2)), or localizes the focus to a different location from EEG, nuclear medicine techniques, PET and SPECT, may be used to guide placement of, or in some cases, replace subdural electrodes (1–3) for further study. For defining an epileptogenic focus (EF), ictal SPECT is the most sensitive study, followed by interictal PET and interictal SPECT (1).

## PET

### Introduction and Technique

PET uses tracers labeled with positron emitters to visualize and quantify cerebral metabolism. The usual tracer is 2-deoxy-2-[18F] fluorogluucose, or FDG, a glucose analogue. Formerly used more extensively, it has been largely supplanted by high-quality MRI. In addition to localizing the EF and suggesting prognosis (particularly for suggesting seizure freedom with a focal abnormality) (4) it can detect subtle anomalies such as focal cortical dysplasia (2). As PET may often not match MRI and EEG, all positive regions should be considered for electrode placement (4).

Unfortunately, tracer availability is somewhat limited by the half-lives of the atoms they are attached to. While

SPECT tracers can be obtained from a generator good for a week, PET tracers used in clinical epilepsy imaging must be made by a cyclotron. The most commonly used positron emitter, F-18, has a half-life of 108 minutes, and others have even shorter half-lives (20 minutes for C-11). While F-18-labeled tracers can be bought and transported, C-11 tracers must be manufactured by an on-site cyclotron (2).

PET has superior spatial resolution (about 4–10 mm) (1) than SPECT, but as brain glucose uptake is slower (over 30 to 40 minutes) (5) and since FDG-PET reflects metabolism during the uptake phase, ictal studies are difficult to obtain. PET scans are thus usually interictal (6). The patient is monitored with continuous electroencephalography (cEEG) during the scan (and/or the 45- to 60-minute uptake between injection and scan) to avoid accidentally performing an ictal PET study (1,4). Ideally, the patient should be seizure-free for 24 hours, although 2 to 12 hours is considered acceptable in some centers (1).

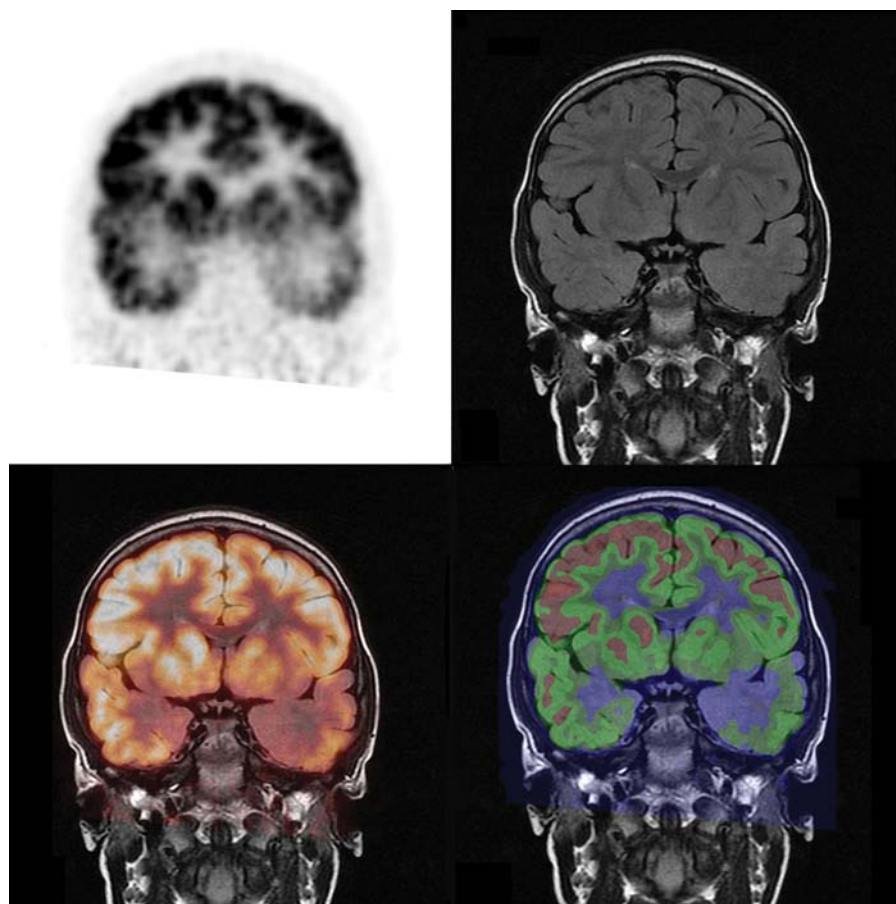
Interictal PET displays decreased activity in the affected area (Figure 21.1) reflecting hypometabolism, for unclear reasons (probably neuronal loss or functional disturbance) (1). Ictal PET scans that have been performed demonstrate significant hypermetabolism (3,5), but the mix of ictal, post-ictal, and interictal states usually due to proposed propagation is hard to interpret (4).

Whole-body effective dose for a PET of the brain is about 14.1 millisieverts (mSv) for a standard 20 microcurie (mCi) dose; this is about equal to a CT scan of the abdomen and pelvis (7).

### Interpretation

The actual scan is usually evaluated visually. Quantitative analysis, using standardized uptake value (SUV), may be used as an adjunct (5). Usually, the most hypometabolic area is assumed to contain the epileptogenic zone (8), with relative temporal lobe hypometabolism of at least 15% to 40% shown to correlate with seizure-free outcomes (1). The onset zone is usually at the margin of the hypometabolic area (2,6).





**FIGURE 21.1** Positive PET scan with hypometabolism in the left temporal lobe, corresponding to hypometabolic region. Upper left: PET image, upper right: MR image, lower left: fusion image using “hot iron” color map, lower right: fusion image using “rainbow” colormap. Note the additional decreased metabolism in the ipsilateral basal ganglia.

Findings may be related to semiology: a study of complex partial seizures found that hypometabolism was limited to the epileptogenic zone in focal limbic seizures, included the limbic cortex in widespread limbic seizures, included the extralimbic frontal lobe with posturing, and included cerebellum and parietal lobes with secondarily generalized seizures (3). Interictal hypometabolism in the putamen is associated with ictal dystonic posturing (4).

### *Temporal Lobe*

The most common focal site of seizure onset is in the temporal lobe. It may be mesial, localized in the hippocampus and due to sclerosis, or lateral, usually neocortical in origin, due to a focal lesion or other cause. Mesial and lateral sites are difficult to distinguish on PET due to spatial resolution (4,5), volume averaging, and widespread temporal lobe hypometabolism in refractory mesial epilepsy (4).

Hypometabolism usually extends outside the lesion itself, although it is less severe extratemporally (4,5). Common sites are the ipsilateral temporal lobe, and less often the frontal (particularly insular and inferior frontal (4)), parietal, and occasionally contralateral temporal lobes (5), as well

as, commonly, the dorsal thalamus (4). Mesial TLE specifically may involve the mesial and anterolateral temporal cortex, as well as the basal ganglia and thalamus (1,4), and more rarely the occipital lobe (4). Refractory patients have more widespread disease; conversely, nonrefractory TLE patients may have a normal PET (4,5). The inferolateral temporal lobe is a common site in MRI lesion negative disease (1).

Over time, the volume and severity of hypometabolism in mesial TLE increase (4). Executive function deficits and depression may be associated with orbitofrontal and prefrontal cortex abnormalities, with more frequent seizures causing worse impairment and larger abnormalities on PET; seizure control may decrease the size of these areas, and they may improve after surgery (3,8). Bilateral temporal lobe hypometabolism is more commonly associated with bilateral, diffuse, or extratemporal seizure onset and bilateral or diffuse MRI abnormalities (3,5). These patients have a lower probability of seizure remission after surgery (3,5) or medical treatment (3), and more cognitive deficits (3).

Children (but usually not adults) may have interictal hypermetabolism (4). Occasionally (1% to 2%) hypometabolism is seen contralateral to the intracranially recorded

site (3,4), possibly due to subclinical epileptiform activity (5), prior surgery, and/or imaging artifacts (4). One way to distinguish focal hypermetabolism from contralateral hypometabolism may be quantification of temporal and occipital metabolism (4). While antiepileptic drugs will decrease metabolism, they will generally do so in a global fashion (4,5), so underlying asymmetries and bilateral symmetric abnormalities will still be visible (4).

### *Extratemporal Lobe*

PET is less sensitive in the extratemporal region, particularly if MRI is normal (4). Extratemporal seizures tend to spread rapidly, so a rapid injection for ictal SPECT becomes more important (5), and detecting the precise focus is more difficult. However, PET can still be useful in guiding subdural electrode placement (5). The border with normal tissue is more gradual (4,5); if there is no lesion, the area may be quite small (4). Frontal lobe epilepsy frequently has a normal PET scan (3). If not, hypometabolism may be quite widespread, including ipsilateral temporal and parietal lobes and occasionally the thalami and basal ganglia (4,5). Parietal lobe foci appear to be more difficult to locate (3).

### *Aids to Interpretation*

Potential aids include coregistration with MRI and voxel-based comparisons with normative data (2). These are particularly useful in extratemporal epilepsy (8).

Coregistering or fusing PET data with a structural MRI can help identify subtle findings such as cortical dysplasias, either by themselves or in association with tumors, and improve delineation of the epileptogenic zone for surgical planning (9). In general, the PET and MRI have to be registered by commercial software (most conventional PACS systems cannot do this well), which frequently allows for display of a fused image as well. A rainbow-color map protocol using a 15% difference corresponding to a color change and SUV calculation with differences of 10% considered significant has shown some effectiveness in the detection of focal cortical dysplasia (6). The resolution is superior to SPECT, but partial volume correction remains useful (8).

In statistical parametric mapping (SPM), each pixel is treated as a z-score using the mean and standard deviation for that patient's overall study. Initial findings have shown successful lateralization and correlation with seizure duration, with the anterolateral temporal region being more important in predicting response to surgery (3). SPM may also be more useful in identifying bilateral abnormalities (3), particularly if asymmetric (4). Some authors suggest using a volume threshold to avoid focusing on very tiny, statistically insignificant foci (4).

## **Validity**

### *Temporal Lobe*

In the temporal lobe, PET sensitivity ranges from 80% to 90% (1,2,6), increasing to 90% with quantitative analysis

(comparing to standard normal) in some trials (1,5). However, its sensitivity in MRI-normal cases may be as low as 44% (8). Concordance with the ultimate site of resection producing relief is high at 96% (10). Some preliminary work suggests flumazenil (FMZ) may be more effective at determining the area to be resected (5). As this is a C11-tracer, availability is limited to centers having a cyclotron.

Postsurgical outcomes are better with more severe abnormalities restricted to the temporal lobe (3,4) (especially mesial (3,5)), a single focus of hypometabolism (4) ipsilateral to the resection site (3,4,6,8), a greater degree of asymmetry (3,8), a greater portion of the hypometabolic area resected (2–4,6), white matter changes on MRI (3) and no or ipsilateral (versus contralateral) thalamic asymmetry (3). Conversely, extratemporal and bilateral temporal hypometabolism make postsurgical seizure control less likely (4). A lack of asymmetry may indicate extratemporal or bilateral foci (3). Essentially, the more likely it is that the temporal lobe is *the* problem, the more likely removing a portion of the temporal lobe is to help.

In some cases of refractory mesial TLE, use of intracranial electrodes may be avoided if there is unilaterally predominant hypometabolism when extracranial EEG electrodes show ictal onset from the ipsilateral temporal lobe, MRI is normal, nonspecific, or localized to the ipsilateral temporal lobe, and other data are not discordant (4). However, simply because the most severe abnormality on PET is in a temporal lobe does not indicate that all seizures arise from that location; thus, no other contradictory data should be present. If the EEG is nonlocalizing, intracranial electrodes may still be necessary (4).

### *Extratemporal*

PET sensitivity for extratemporal epilepsy is lower than for temporal lobe epilepsy. It is somewhat higher at 70% to 90% than the sensitivity of 30% to 80% for MRI (6) (although concordance may be somewhat lower at 68% (10)). In the case of frontal lobe epilepsy, sensitivity is lower at 45% to 73%, and even lower at 36% for MRI lesion-negative patients; performance may be somewhat higher in children (5).

Patients with extratemporal cortical hypometabolism ipsilateral to the site of surgery generally had a lower frequency of successful surgery than those with temporal cortical hypometabolism (45%–60% vs. 75%) (3,5,8). PET is of more utility in guiding subdural electrode placement than in detecting the epileptic foci (EF), due to the relatively rapid spread (5). In addition, work using high-resolution registration has suggested that small mismatches between hypometabolic and epileptogenic areas are common in extratemporal epilepsy. PET may also find additional foci (4).

### *Cortical Dysplasias*

PET has been shown to be particularly useful in cases of multiple or focal cortical dysplasias (FCD) that are often subtle on MRI. It is 75% to 100% sensitive (3,9) and 78% concordant with MRI (1) in localizing areas with FCD (usually

appearing as a hypometabolic zone); more areas (and more extensive areas) may be visible with PET than with MRI (1,6). Sensitivity for cortical dysplasia in general may reach 70% to 80% with coregistration (6), and coregistration will allow for localization of an EF in 33% of patients with negative or discordant EEG and MRI (6).

### Other Uses

PET is useful in neonates with intractable seizures of unknown etiology. A focal abnormality suggests a focal developmental abnormality, whereas diffuse abnormalities suggest a metabolic cause (11).

PET has been shown to detect abnormalities not seen on MRI in cryptogenic infantile spasms (West syndrome). Surgical removal of abnormal foci of cortical dysplasia can stop seizures and sometimes reverse developmental arrest (3,4,11), particularly if PET and EEG are concordant and/or PET anomalies normalize on medical therapy (4).

PET in Lennox-Gastaut syndrome may suggest EF (3). Cortical tubers are hypometabolic on FDG-PET (to about 30% to 50% vs. the other side) (1), and show *increased* uptake with 11C-AMT—in two-thirds of epileptogenic cases (5). In Sturge-Weber, PET shows hypometabolism ipsilateral to the nevus and demonstrates the extent of involvement in the cortex below, guiding resection and detecting contralateral hypometabolism when hemispherectomy is considered (3–5). Patients with cutaneous but no intracranial anomalies have a normal PET (4). Patients with GLUT1 transporter deficiency show generalized reduction in FDG activity, but relative preservation in the basal ganglia (4). PET is generally not used in primary generalized epilepsy to exclude surgical candidates, as such patients are usually diagnosed from history and EEG; if performed, interictal FDG studies are usually normal, as is sometimes the case with secondarily generalized epilepsy (4).

### New Directions

Simultaneous acquisition in a PET-MRI system may improve coregistration, as well as helping to determine motion correction, or obtain multifunctional imaging such as combining PET ligand uptake with processes such as arterial spin labeling, MR spectroscopy, or blood oxygenation-level-dependent imaging (12).

While FDG is the most common tracer used, other tracers can be used to investigate other pathways, such as 11C-FMZ for GABA-A receptors or 11C-alpha-methyltryptophan (AMT), a serotonin precursor (1). Many of these are limited by use of 11C as a radionuclide, whose half-life of 20 minutes not only allows for a smaller radiation dose but also limits administration to institutions with a cyclotron.

Much like FDG, FMZ binding is significantly lower in the EF (1,16), the degree of which may correlate with seizure frequency (3). 11C-flumazenil may have a more restricted area of hypometabolism than FDG (1,9,11), and

may be more sensitive for contralateral abnormalities (9) and mesial temporal sclerosis (11). Changes have been seen in the thalamus in temporal lobe epilepsy and contralateral cerebellum in frontal lobe epilepsy as well (3). Larger regions of FMZ uptake may correlate with seizure frequency (1), and periventricular uptake before surgery may correlate with a poor outcome (1). It may be more accurate in extratemporal, in particular, frontal, epilepsy as well (1,3).

11C-AMT has shown to be specific for seizure foci, particularly in tuberous sclerosis (8), as described previously, where epileptogenic tubers have a higher uptake (1). It may also be useful in identification of nonresected epileptogenic cortex (5) or developmental malformations (11).

Among the many other tracers in investigative use are 11C-carfentanil and 11C-methylnaltrindole for opioid receptors and 18-MPPF, a selective 5-HT1A agonist (3). Opioid-receptor tracer uptake may be more localized than FDG and may increase postictally. Synaptic opioid levels may correlate with seizure activity (3). 18-MPPF, a selective 5-HT1A agonist, may be more sensitive and accurate (3) in MRI lesion-negative temporal lobe cases.

## SPECT

### Introduction and Technique

SPECT evaluates regional cerebral perfusion (rCP), which is generally coupled to metabolism. The seizure zone is hyperperfused during epileptic activity because of local neuronal hyperactivity (8), whereas it is hypoperfused between seizures (6). SPECT, unlike PET, allows for ictal imaging (13). Spatial resolution is generally not as good as PET (about 8–10 mm) (6).

Of the three FDA-approved radiopharmaceuticals, one (IMP, or isopropyl-iodo-amphetamine) is primarily used in Japan. The other two, both using Tc-99m as the radionuclide, are HMPAO (hexamethylpropylamine oxime, Ceretec, GE Healthcare, Chalfont St Giles, UK) and ECD (ethyl cysteinate dimer; Neurolite, Bristol-Myers Squibb, North Billerica, MA). The Tc-99m radionuclide has a longer half-life (6 hours) and is obtainable from generators, allowing for easier availability relative to PET. In general, the compound is bound to a specific area of brain on its first pass through and remains there (being converted to a polar metabolite) for several hours. The patient can thus be injected during a seizure, and the SPECT scan be done hours (up to 2 (13) to 4(1)) later when the patient has recovered and is cooperative. One important difference between the two compounds is that HMPAO must be used within 20 to 30 minutes of its preparation, whereas ECD is stable for 4 to 6 hours. ECD is also rapidly excreted renally, decreasing radiation burden and allowing for administration of a larger amount of radiopharmaceutical with the same overall dose (5). In the experience of the authors, ECD produces a much better quality of image with much higher sensitivity.



As the injection needs to be performed quickly after seizure onset (1), seizures should be quickly detected by staff, the person injecting the tracer should be familiar with the seizures, and a preexisting, well-maintained intravenous line should be present (1). High-quality SPECT may be difficult to successfully acquire, as frequent seizures may make a true interictal scan difficult, and associated problems such as learning and behavioral problems may complicate accurate identification of seizure onset. Pediatric patients in particular have a large proportion of extratemporal epilepsies, with short duration and rapid spread (5).

In general, the patient is admitted for video EEG (vEEG) monitoring with ictal and interictal scans planned during the same admission. The patient (or their parents) is consented. The tracer is injected in the telemetry suite, with the radiopharmaceutical in a lead-shielded syringe containing the prescribed dose. A vial in a lead container with more of the radiopharmaceutical is available as well, so a sufficient amount of tracer to replace the decayed tracer can be withdrawn if necessary. A sheet is used for displaying an appropriate volume to be withdrawn to account for radioactive decay (5). Note that the compound must be discarded after 6 hours if the patient does not have a seizure, so frequently the radiopharmacy will have to send up to two doses during the day (13).

The exact times of tracer injection and EEG onset of seizure should be noted so one can determine if the injection is ictal, peri-ictal, or postictal (5). Seizures should last at least 5 to 10 seconds, and (ideally) the SPECT tracer should be injected less than 20 seconds (8) after the seizure starts, although 45 (13) to 90 seconds (10) is acceptable. Injection after the seizure—postictal SPECT—is less sensitive (13), as focal hyperperfusion becomes hypoperfusion. This postictal switch is generally complete at 100 seconds after the seizure ends (8). While ictal scans are generally considered superior, a postictal scan may retain some value, at least in temporal lobe lesions. One study showed a pattern of mesial hyperperfusion accompanied by lateral hypoperfusion having a 97% PPV; a postictal injection retains a 70% to 90% sensitivity in mesial TLE (5).

Imaging itself usually takes about 20 to 30 minutes (13). Children 1 to 4 years old (or older if uncooperative) are generally sedated, whereas children less than 1 year of age are fed and wrapped before the scan (5). In general, the patient should be sedated on the ward before arriving in the imaging department (5).

The interictal scan, conversely, is usually performed when the patient has been seizure-free for at least 30 minutes (usually on a different day). The patient is usually injected in the imaging department for this scan, with sedation if necessary for a pediatric patient. The interictal scan is less useful by itself, but aids the localization of the EF together with the ictal scan by visual assessment or subtraction (5).

Images can be reconstructed at any angle (13); however, data should be reconstructed after reorientation parallel to the anterior–posterior commissure line with another set of data reconstructed parallel to the long axis of the temporal lobe (5). A continuous color scale is recommended, to avoid

overestimation of tiny asymmetries. A high-resolution or fan-beam collimator should be used (5).

Whole-body effective dose equivalent from a 20 mCi dose of Tc-99m HMPAO is 6.9 mSv, whereas that from 20 mCi of Tc-99m ECD is 5.7 mSv. This is about half the dose for a CT scan of the abdomen and pelvis, and 3 to 3.5 times that of a head CT scan (7).

## Interpretation

In general, areas of abnormal activity are described as being hyper- or hypo-perfused, as compared with a reference set (cerebellum, if unaffected, or average cortical activity in the same slice). A SPECT study showing increased ictal relative cerebral perfusion (rCP) and decreased interictal rCP in the same area strongly suggests that a lesion is the cause of seizures (13); subtraction of the interictal from the ictal scan can help visualize this (2). If multiple “hot” areas are visible, the largest and “hottest” area of ictal hyperperfusion is assumed to represent the ictal-onset zone (8). Note that it takes 15 to 20 seconds for the tracer to reach the brain from intravenous injection, so areas of propagation are usually seen as well (8) (Figure 21.2).

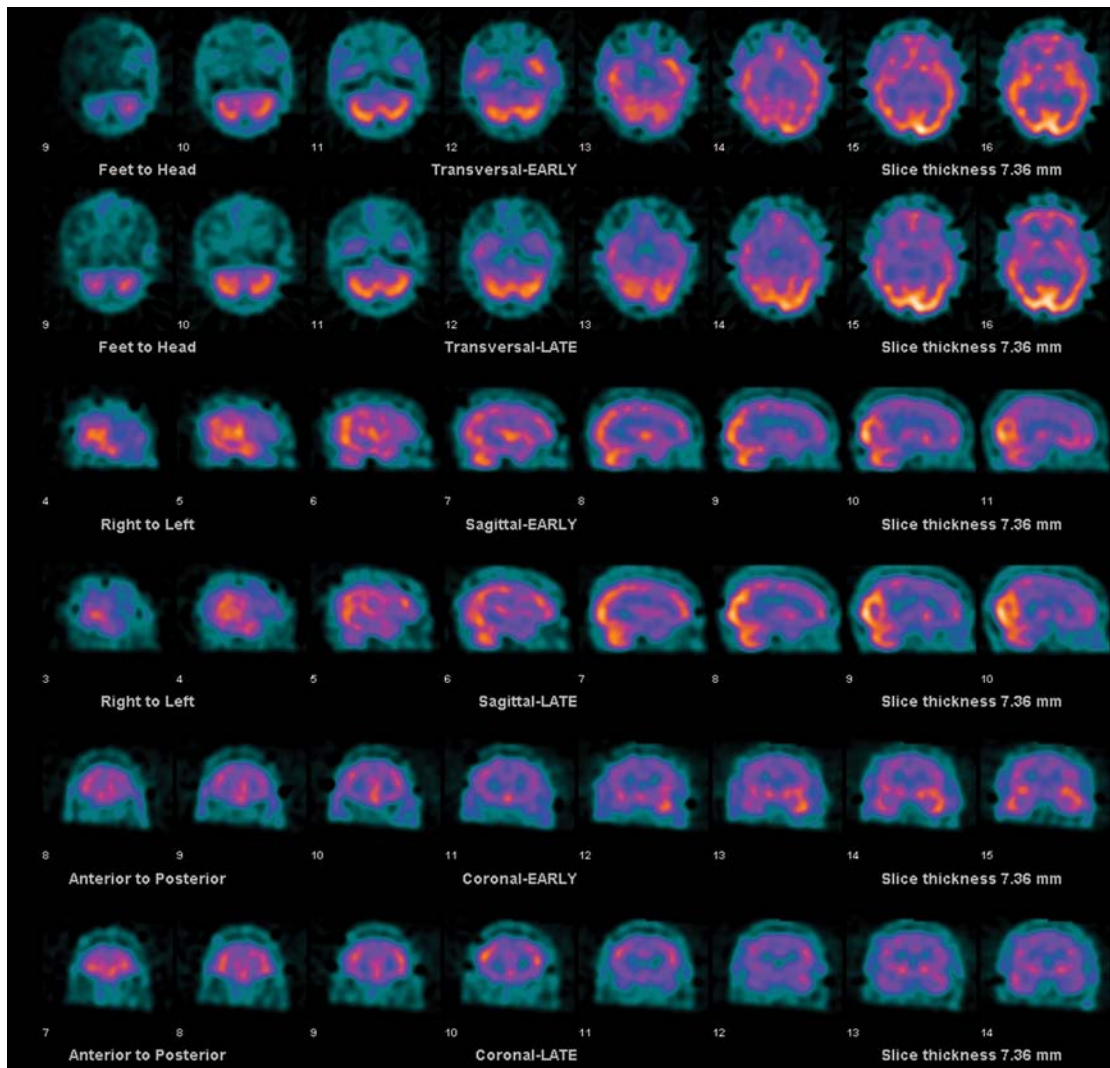
### Temporal Lobe

Interpreting the study should take into account time of injection. In cases of TLE, seizure activity tends to propagate to the contralateral temporal lobe and ipsilateral insula, basal ganglia, and frontal lobe (8). Specifically for mesial temporal sclerosis, one may see hyperperfusion in the whole temporal lobe and possibly orbital and frontal cortex within 15 seconds of injection. Slightly more delayed hyperperfusion may be seen in the lateral temporal, orbital, or motor cortex, basal ganglia, or both temporal lobes. Hypoperfusion of the lateral temporal lobe with persistent hyperperfusion of mesial structures occurs within 4 minutes after the end of the seizure. Finally, hypoperfusion of the whole area may be seen 15 minutes after the end of seizure (5).

Correlations between pathology and hyperperfusion patterns have been made. Mesial temporal lobe lesions tend to show well-localized hyperperfusion involving the mesial and lateral temporal lobes. Lateral temporal lobe lesions show more bilateral changes, possibly as a result of connections to the opposite amygdala via the anterior commissure. The changes are nonetheless more prominent on the ipsilateral side (5). MRI lesion-negative patients with good outcomes have shown a pattern of hyperperfusion restricted to ipsilateral antero-mesial temporal structures (5). However, due to issues of spatial resolution, differentiation between mesial and lateral temporal lobe lesions is difficult.

### Extratemporal Lobe

The most common pathology in this case is focal cortical dysplasia, and, as with PET, one aims to confirm the importance of the visible lesion and to localize the area for subdural grid



**FIGURE 21.2** Ictal (upper rows—"EARLY") and interictal (lower rows—"LATE") SPECT, with focus of increased activity seen in left temporal lobe on ictal imaging, which is not present on interictal imaging. In this case where SPECT images are being interpreted without reference to an outside image, ictal and interictal series are lined up in each of the three reference planes, with manual adjustment of each series for better correspondence.

placement (5). A particular problem with extratemporal seizures is their short duration (at least 10 to 15 seconds is necessary for accurate localization). As perfusion changes do not persist past the seizure (unlike temporal lobe seizures), postictal injections are not useful (5).

Patterns of hyperperfusion differ with time of injection, and include (ideally) a large and intense hyperperfused area at the lesion itself (in early injection), a less intensely hyperemic area at the actual lesion with the most intense uptake at a distance (at later injection times), and a complicated, multilobulated pattern (also at later injection times), seen in frontal lobe seizures with fast propagation. In frontal lobe lesions, the largest cluster of ictal hyperperfusion usually includes other brain regions as well as the ictal-onset zone (8).

Patterns of propagation are somewhat distinct for extratemporal epilepsies as well. Occipital seizures quickly spread

to both temporal lobes, making early injection important. An anterior spread is often associated with sensory and motor manifestations (5). Frontal lobe epilepsy often demonstrates hyperperfusion in ipsilateral basal nuclei and contralateral cerebellar hypoperfusion (5). A larger area of hyperperfusion than the tumor itself may be seen in dysembryoplastic neuroepithelial tumour (DNET) (5). Focally increased uptake on ictal SPECT in tuberous sclerosis corresponds to sustained rhythmic fast activity on an ictal EEG (5). This may be useful in cases of multiple tubers (5).

#### *Aids to Interpretation*

With SPM, the ictal SPECT is compared to a series of normal scans, and each voxel is analyzed with statistical tests to identify regions of significant change. One advantage of this technique is that it may make interictal scans unnecessary

(one can compare with the standard normal instead). However, there are issues of regional alterations in blood flow unrelated to seizure activity, and particularly in the pediatric population under 6, developmental stages of the brain may make the technique less accurate (15).

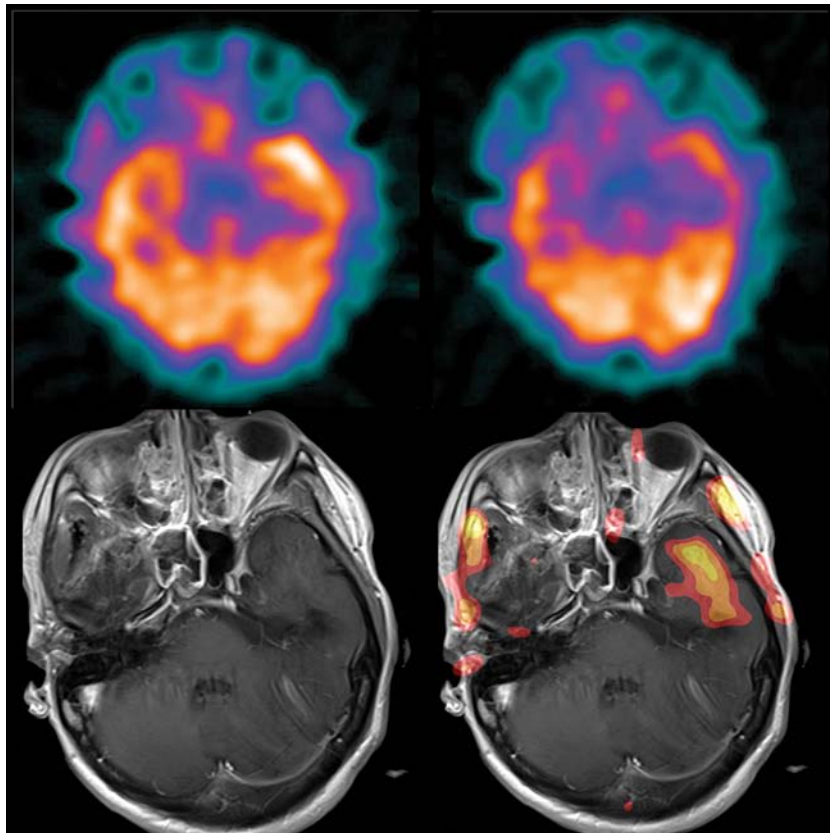
SISCOM (subtracted interictal SPECT coregistered to MRI) is a procedure where ictal and interictal SPECTs are subtracted and the result coregistered to an MRI (Figure 21.3). It may be useful in presurgical evaluation when MRI is normal or localizes discordantly with EEG, multiple epileptogenic lesions are present (such as in bilateral mesial temporal sclerosis or bilateral cortical dysplasias) or to identify a target for placement of intracranial EEG electrodes. SISCOM is particularly useful in malformations of cortical development, as the dysplastic areas are not definitely known to be epileptogenic yet (6,13), in tumors such as DNET where a surrounding area of dysplasia may be present (5), for extratemporal epilepsies, and cases of rapid seizure propagation (8). As with PET, coregistration with MRI may reveal previously occult abnormalities; however, SPECT is more commonly used to help choose intracranial electrode placement by providing information on secondary spread of ictal activity (2). Another aid is voxel-based analysis of studies—specifically, calculating

the difference between ictal and interictal cerebral blood flow as a Z-score of the variation between scans using the mean and standard deviation of the differences in all brain voxels (2,8). In the case of SISCOM, careful quality control of registration (assessment of motion and registration errors) becomes important to avoid false negatives and positives. SISCOM assessment should be concordant with visual assessment (8).

### Validity

Among the nuclear medicine methods, ictal SPECT is the most accurate, with a sensitivity of 96% reported in one meta-analysis (1). In the case of complex partial seizures in particular, ictal SPECT is 71% to 93% sensitive (over 90% for temporal lobe seizures) and has 95% PPV (13). Localization is correct in 80% to 90% of cases (5). Concordance with ultimate site of relief-producing resection is very high (10). Early postictal SPECT retains a sensitivity of 75% (8). Interictal SPECT is less sensitive, with sensitivity about 50% for temporal lobe seizures (6).

Neocortical epilepsy, including extratemporal limbic and extralimbic epilepsy, has a very low sensitivity for interictal SPECT (15% to 30%), but a reasonable sensitivity for



**FIGURE 21.3** SISCOM. Ictal, interictal, MRI, and fused subtracted images (same patient as Figure 21.2). SISCOM projects the area of ictal over interictal increase over the MR, showing the area of greatest discrepancy (in favor of higher intensity in the ictal image) projecting over the left temporal lobe.



**TABLE 21.1 Comparison on PET and SPECT**

PET	SPECT
Interictal only	Ictal and interictal
Can be injected between seizures	Must inject immediately after or during seizure; must admit for several days of monitoring
Useful for detecting cortical dysplasias; 11C-AMT can distinguish epileptogenic and nonepileptogenic tubers if available	Better for extratemporal (and temporal) epilepsies if immediate ictal injection can be performed
WB effective dose: 14.1 mSv	WB effective dose: 6.9 mSv (HMPAO), 5.7 mSv (ECD)

Source: Adapted from Refs. (1, 5–7).

ictal SPECT (>75%) (6,10) and good concordance (92%) (10). One reason for the relatively better performance of SPECT vis-à-vis PET in non-temporal-lobe epilepsy may be the preponderance of neuronal migration disorders, in which PET can have a variety of appearances (10). However, as extratemporal seizures are frequently brief, often a postictal SPECT is actually performed, which has a lower sensitivity of 20% to 50% (6). A comparison of PET and SPECT is presented in Table 21.1.

## fMRI

### Introduction and Technique

fMRI can help to localize eloquent cortex (cortex whose loss will result in language, sensory, or motor deficits). Frequently, in the surgical treatment of temporal lobe epilepsy, the hippocampus must be resected, and establishing which hemisphere language and memory are in before surgery is important (14).

The current standard fMRI technique is BOLD (blood oxygen-level dependent) imaging. In active neurons, blood flow increases, deoxyhemoglobin concentration decreases, and fMRI signal increases (appears bright). Signal changes are subtle, and so a high-field (3T) system is preferred, and statistical analysis of signal data required (14).

The basic idea is to identify areas responsible for functions such as language, memory, and motor function by identifying areas active during a certain activity. This is usually done by having the patient perform a task with an experimental condition (which uses the appropriate brain function) and a control condition (which does not). Usually conditions are presented in blocks of 20 to 40 seconds run over 3 to 6 cycles of alternating experimental and control conditions (block design), with image analysis programs searching image data sets acquired during each condition to find significant differences between the two conditions. Some processes are better studied using event-related designs, where brief individual events are studied; this is more useful if some events do not result in a successful response (failure to encode a memory item) or for cognitive tasks. Thus, analysis can be isolated to only successful events, yielding

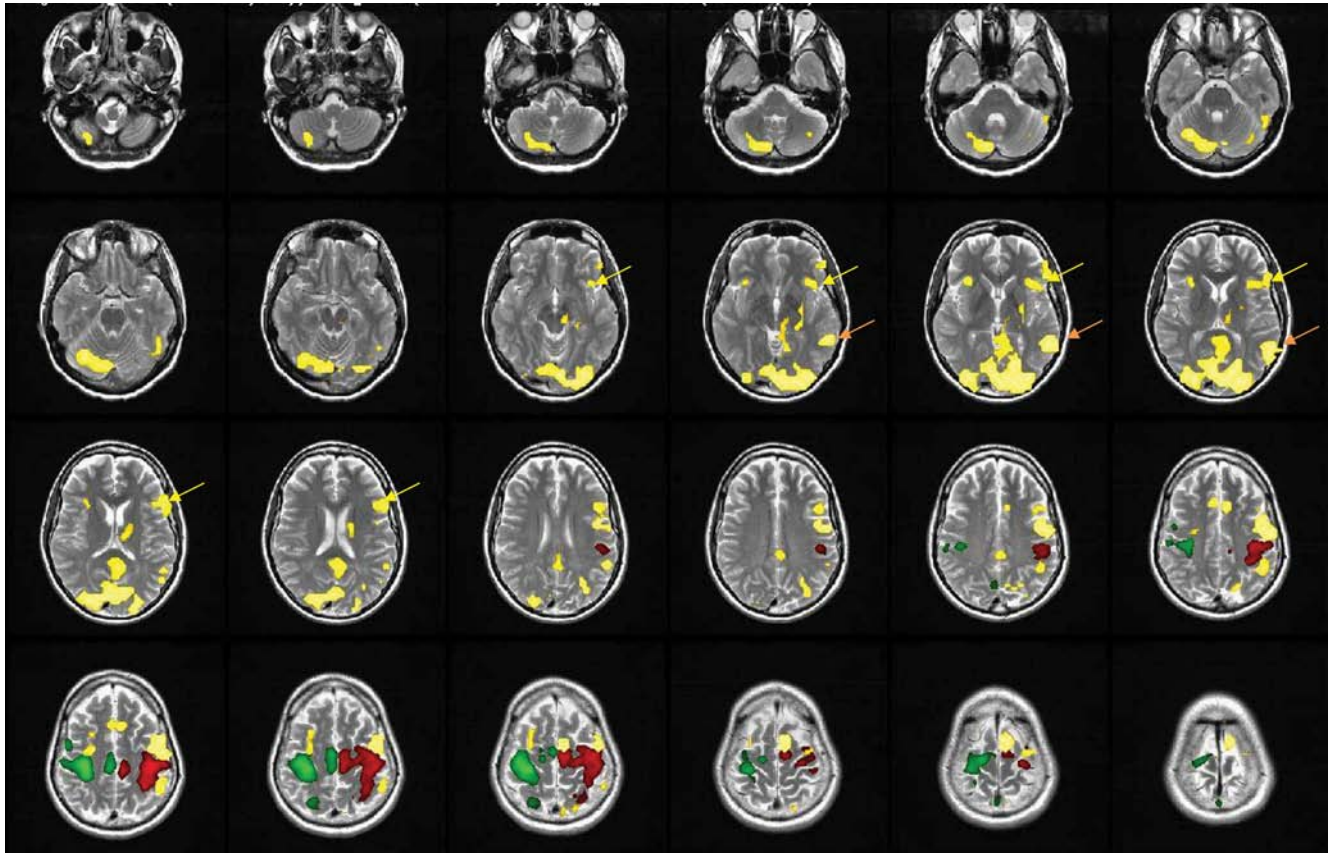
greater power to show a task-related effect. Usually 27 to 30 events are necessary (15) (Figure 21.4).

### Motor and Sensory Localization

Motor function is often mapped together with language in the same examination, as a hand motor task may take as little as 2 min. The usual task used for localization of primary motor cortex is finger tapping (which produces the least motion artifact). Supplementary motor cortex can be identified using more complex movements, though it is often visible with the simple finger tapping or hand squeeze task. Sensory proprioceptive cortex can be specifically identified by brushing the face, hand, or foot, and is often seen with a motor task, as proprioception during movement causes activity in the postcentral gyrus, which blends with the activity in the precentral gyrus. In addition, because fMRI often localizes postcapillary venules associated with active brain tissue rather than the brain tissue itself, activation during motor task is often centered about the central sulcus and referred to as “sensorimotor” activation. Auditory cortex may be localized by presenting tones, and visual cortex with a flashing checkerboard presentation. Three cycles of 20 seconds may be all that is necessary (15).

### Language Lateralization

Language lateralization is the most common indication for fMRI (14). The anterior temporal lobe and mesial structures such as the hippocampus are commonly resected in epilepsy surgery, which can cause language and memory deficits (14). Verbal memory is subserved by the language-dominant hippocampus, and its resection increases the risk of amnesia (14). While the dominant expressive and receptive speech areas are usually left-sided, many epilepsy patients (especially if left-handed, having onset of symptoms or brain injury before 6 years of age, or those with developmental lesions) have atypical language lateralization (14,15). In cases of pediatric patients with large, hemispheric epileptogenic lesions who may undergo functional hemispherectomy, functions are frequently reorganized. Knowledge of



**FIGURE 21.4** Superimposed on T2-weighted axial images are yellow and orange areas representing language, with receptive (orange arrows) and expressive (yellow arrows) speech areas indicated, as well as the right hand motor area (red) and left hand motor area (green).

the particular pattern of reorganization would be of paramount importance in considering future interventions (14).

Previously, the intracarotid amobarbital procedure (IAP, also referred to as the Wada test) was used to determine language hemispheric dominance (14). Intraoperative cortical mapping or intracranial electrode stimulation can also be used if the area to be resected is in the same hemisphere and in proximity to the putative language areas (14). In a recent meta-analysis, fMRI was shown to correlate strongly with the Wada test—about 89% for right TLE and 72% for left TLE (1), with overall 83% sensitivity and 86% specificity (16). A few studies have shown fMRI correlation with intraoperative mapping of language areas (14,17,18). In many centers, Wada testing is reserved for cases in which the fMRI was inconclusive or in which memory lies at significant risk. Rarely, Wada tests are performed when fMRI cannot be performed due to inability to cooperate, either behavioral or perceptual (such as blindness or deafness) (19). In surgery on early-onset epilepsy patients, invasive techniques such as intraoperative cortical stimulation with invasive electrodes are still necessary due to the high incidence of atypical lateralization (14). A comparison of the IAP and fMRI is presented in Table 21.2.

Language paradigms used in fMRI are performed over a block of time and compared to rest (15). Expressive language systems usually utilize verbal fluency (either free—generating a list of words falling into certain categories—or paced—presenting a word and asking for words with a given relationship, such as rhyming or association, in response). For receptive language systems, a story may be read or listened to (15). Usually, a panel of tasks is useful, using different aspects of language. Using comprehension tasks is important, given that the surgical target is frequently in the temporal lobe. Agreement with the Wada test is usually less with neocortical patients with normal MRI (15).

Language dominance can be usually assessed visually. If quantitation is desired, a laterality index (LI) of activated voxels in the left minus the right regions over the sum of the left and right can be used. Most studies on the subject consider an LI of 0.2 to be indicative of left-dominance. In right dominance, the LI is less than -0.2. Activation with LI between 0.2 and -0.2 is considered bilateral. Dominance may be mixed between expressive and receptive speech, with dominance on opposite sides. Truly bilateral cases may require invasive methods such as the Wada test (or ECS) to assess for concordance.

TABLE 21.2 Comparison of IAP and fMRI

WADA TEST	fMRI
Radiation use, risk of stroke, and hematoma	No radiation use
Limited if vascular supply abnormal	Patient must be cooperative, not claustrophobic, safe for MR
	Allows acquisition of normal data

The physiologic basis of the BOLD test can be disrupted by critical carotid stenosis, a vascular steal adjacent to AVMs, large gliomas with marked mass effect, or a postictal state. These may misidentify dominance. Postponing an fMRI study after a series of seizures or immediately postictally should thus be considered (15).

### Memory Evaluation

Mesial temporal sclerosis itself (as well as its resection) may cause visual deficits because of adjacent optic white matter pathways or verbal memory deficits, depending on which hemisphere is language dominant (14). Memory lateralization is usually assessed by neuropsychological evaluation. The IAP is usually reserved for high-risk cases (14). Memory evaluation using fMRI remains in development for a number of reasons. The hippocampus is a challenging area due to susceptibility artifact from the nearby temporal bone and paranasal sinuses. Parallel acquisition techniques may help reduce this (14,15). Memory processing is significantly more complex than language and uses a larger number of areas, including the prefrontal cortex and mesial temporal structures such as the posterior body of the hippocampus, parahippocampal, and fusiform gyri (14). Activation in encoding or recall tasks is usually bilateral (14). Few studies have, as of yet, compared memory fMRI with the Wada test (14). In general, greater activation in the resected formation is associated with greater deficit, regardless of contralateral activation (15).

### Localization of the Ictal Focus

The BOLD contrast in fMRI studies shows areas of hyperemia during a seizure that spread to other areas with seizure propagation. Changes in signal in distant areas are even seen before a seizure occurs (14). However, motion artifacts during seizures confines applicability to partial seizures without motor manifestations. Moreover, simultaneous EEG is necessary to correlate functional data with electrical brain activity, requiring specialized MR-compatible EEG equipment and analysis techniques, limiting clinical applicability at present (14,15).

Functional imaging is an important part of the evaluation of patients for epilepsy surgery. When brain MRI abnormalities are not evident, and sometimes even when they are, functional imaging can help to further confirm that the correct EF has been identified. PET and SPECT can identify functionally abnormal areas, whereas fMRI helps identify certain eloquent brain areas. Each type of imaging has particular advantages and often more than one type of functional imaging may be needed in a particular patient.

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# Wada Test

*Adriana Palade*

## 22

### C H A P T E R

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Patients with medically refractory epilepsy commonly undergo a Wada test (or intracarotid amobarbital procedure) as part of the presurgical workup for anterior temporal lobectomy. The Wada test is used to predict whether patients are at risk for postoperative amnesia or memory decline, to assess the risk of material specific memory deficits, and to lateralize memory dysfunction.

#### HISTORY

In 1949, Juhn Wada described the use of intracarotid amobarbital injection to determine the cerebral language dominance (1). This procedure was later modified at the Montreal Neurological Institute to also assess hemispheric memory and has since then become a standard component of presurgical evaluation for epilepsy surgery (2).

The cognitive outcome of epilepsy surgery or even tumor resection in the dominant hemisphere depends on the accurate localization and lateralization of the “eloquent” cortex, especially the language area. In addition, the Wada test has been used to predict residual motor functions before hemispherectomy.

However, during the past two decades, there has been a significant shift in the role of the Wada test in epilepsy surgery, such that the test is no longer performed as a routine procedure. Alternative noninvasive methods, most commonly functional magnetic resonance imaging (fMRI) and the evaluation of the available clinical data (seizure semiology, improved MRI quality, neuropsychological data) may provide enough information for language localization or memory reserve capacity determination.

#### PROCEDURE

The Wada test is performed in the radiology suite. Selective internal carotid catheterization is achieved via the femoral artery route. The Wada test is an invasive procedure accompanied by a significant rate of complications in up to 10% of the cases, ranging from encephalopathy (7%), seizures (1.2%),

strokes (0.6%), transient ischemic attack (0.6%), and localized hemorrhage at the site of catheter insertion (3). The intracranial arterial anatomy may vary between patients, with persistent fetal circulation in some, hypoplastic anterior cerebral or vertebral arteries in others, and different amounts of blood flow to the contralateral hemisphere from the internal carotid artery (ICA). Most importantly, the posterior medial temporal lobe is supplied by the posterior circulation to a variable extent, so temporal lobe inactivation may be incomplete.

The dosage of amobarbital injected varies between centers from 75 mg to 150 mg, injected within a short period, typically of 3 to 5 seconds, with a single-bolus technique. The dose should be sufficient to produce anesthesia of the injected hemisphere, which is tested by assessing motor and speech performance during the injection. In preparation for the test, a patient is connected to an EEG machine using the standard 10-20 system of electrode placement. Typical stimulation techniques of eye opening and closure are performed, but none of the activating procedures is necessary. Before the injection, the patient lays on his/her back, raises his/her arms, and begins to count. The patient is instructed to continue counting until told verbally or with nonverbal maneuvers of manual pressure on the outstretched arms to stop counting and put the arms down. Within seconds of injection, the contralateral arm drops as hemiparesis/hemiplegia develops, indicative of an effective injection. When the dominant hemisphere is anesthetized, the patient develops a global aphasia and is mute for a period of 3 to 4 minutes, after which the speech gradually returns, with dysphasic and paraphasic errors seen first.

When the nondominant hemisphere is injected, the patient may continue to count or speak but usually exhibits dysarthria lasting several minutes. Occasionally confusion, inattention, perseveration, or agitation accompanies the hemiparesis and speech impairment, particularly when the language-dominant hemisphere is injected (4). Before administering the test items, especially if the patient is mute, several commands must be followed, such as opening/closing the eyes, raising the hand, or being able to look at

the examiner. Over 18 items are presented during the test, which consist of objects, abstract designs, written words, and phrases to repeat. The patient is constantly asked to recognize each item that is presented and to remember it, allowing the examiner to assess the language function in addition to the memory. Intermittently throughout the test assessment of the strength of the extremity contralateral to the injection site is performed. Within 15 to 20 minutes, all testing items are presented, and simultaneously the contralateral hemiparesis usually resolves and ipsilateral slowing on EEG usually resolves.

Most epilepsy centers inject the site of the epileptic focus first and perform injections of both internal carotid arteries during the same day. It is common practice to record the EEG simultaneously with the Wada test to evaluate the extent of the physiologic effect of amobarbital, consisting of unilateral slowing. The EEG recording is extremely helpful if the patient becomes severely obtunded after injection, which is associated at times on EEG with bilateral slowing. This raises the suspicion of arterial crossover of the medication as an explanation of the obtundation. The clinical and physiologic (EEG) changes induced by amobarbital must resolve before testing of memory function.

## LANGUAGE EVALUATION

### Validity

Cerebral hemisphere dominance for language function was first documented by Broca, who described a patient with a lesion in the left inferior frontal gyrus who experienced expressive aphasia (5). The relationship between the language lateralization and handedness was also established during the same time period. It is well accepted that the left hemisphere is dominant for speech, not only for the majority of right-handed individuals, but also for the majority of left-handed ones and those who are ambidextrous. Nonetheless, the right hemisphere has been demonstrated to be dominant for language in some right-handed individuals who have crossed aphasia, explaining how lesions in the right hemisphere may result in aphasia (6). The right hemisphere is estimated to be dominant for language in 1% to 2% of the normal population.

The Wada test has commonly been described as the gold standard for the determination of cerebral hemisphere dominance for language against which novel language lateralization techniques are judged. However, in many patients, a combination of fMRI studies, ictal semiology, postictal recovery, and baseline neuropsychological measures is able to indicate language dominance with a high degree of accuracy (7,8).

Multiple studies have evaluated the relationship of handedness and language dominance. In an overwhelming majority of right-handed individuals (80%–100%), the left hemisphere is seen to be dominant for speech. There are a few right-handed individuals who are right hemisphere dominant for speech, with a range of 4% to 10%. However, the

presence of a hemispheric lesion is an important influencing factor in language lateralization. If a left hemisphere lesion is present, the percentage of right-hemisphere-dominant subjects and those with bilateral speech representation increases to 12% and 7%, respectively (9). In the absence of a left hemisphere lesion, patients with left or mixed handedness appear to have left hemisphere dominance for speech in 64% to 70% of cases, right hemisphere language dominance in 15% to 20% of cases, and bilateral language representation in the remaining 15%. In the presence of a left hemisphere lesion, the right hemisphere is dominant for speech in 53% and 67% in the two series reported by Rassmussen (9). Bilateral representation was also found in up to 20% of left-handed individuals.

Patients with epilepsy have a much higher rate of altered language lateralization: 22% versus 6% altered lateralization seen in normal controls (10). These patients often have bihemispheric participation in language and increased variability in language dominance. Left-handed patients are most likely to have atypical language representation. Atypical language lateralization is more common in patients who have structural or functional extrahippocampal involvement, an early onset of epilepsy, usually before the age of 6 years (11), a short time period between the initial precipitating injury and onset of habitual seizures, and bitemporal and extratemporal interictal discharges on EEG (12).

### Validation

The Wada test has been well accepted as the study of choice to define hemisphere dominance for language function before neurosurgical resective procedures, especially in epilepsy. It is also used as the gold standard against which novel language lateralization techniques are judged. The majority of these new techniques rely on the analysis of activation patterns during language tasks rather than on the evaluation of behavior and cognitive function following temporary and reversible pharmacological cerebral deactivation.

fMRI language tasks are most widely used in lateralizing language function and the paradigms have been found to provide valuable data in the assessment of hemispheric language dominance in patients with epilepsy (13). However, concerns have been raised about the reliability of these newer techniques in patients with atypical language representation. The interpretation of bilateral fMRI activation patterns is particularly challenging. There are large individual differences in fMRI language activation patterns in patients with atypical language representation demonstrated by the Wada tests (14). In addition, there is interhemispheric dissociation between speech production and comprehension (15). Speech production capacity is more likely to shift hemisphere (away from the seizure focus) than language comprehension. The Wada test can answer one question that the fMRI cannot address: Can a task still be performed if part of a particular hemisphere is removed?

Magnetoencephalography (MEG) is showing some promise in identifying both frontal and temporal language

areas. Transcranial magnetic stimulation was introduced in the 1990s as a possible alternative to the Wada test, but it has been poorly tolerated by many patients and often produces significant discrepancies when compared to the Wada test results. Functional transcranial Doppler sonography in which the blood flow is measured in the bilateral middle cerebral arteries during the performance of a language task also shows good concordance with the Wada test language lateralization and may be better tolerated by special populations (16).

## MEMORY EVALUATION

### Validity

The primary purpose of testing memory during the Wada test is to identify those at risk for a postoperative amnesia.

Memory failure during the Wada test is diagnostic because it evaluates the capacity of the brain to support global, anterograde memory when certain brain structures are pharmacologically inactivated. The prognosis of the postoperative amnesia derives from the assumption that memory performance during the Wada test correlates with everyday anterograde memory, and the short-term effects of the Wada test are sufficiently analogous to the long-term effects of surgery on memory.

The incidence of severe postoperative amnesia after anterior temporal lobectomy is low with only 10 reported cases in the past 50 years. Most were reported before the MRI was available (17,18). Nine of these occurred following dominant temporal lobe resection, and all of the cases showed evidence of contralateral dysfunction or atypical dominance independent of the Wada test. However, the predictive value of the Wada test with regard to postoperative amnesia may not be known.

Criticism of the Wada test in predicting postoperative amnesia has increased after reports of false positive results. There are frequent reports in the literature of patients who failed both ipsilateral and contralateral injections during a Wada test and underwent unilateral temporal lobe resection. None of these patients developed global amnesia, although some reported postoperative memory decline. A large number of these patients also demonstrated a greater than 90% improvement in seizure control postoperatively (19,20). In addition, there are numerous reports of patients who failed the Wada test memory assessment but subsequently passed a repeat procedure and underwent surgery without any subsequent memory impairment (21). This certainly raises questions about the validity of this test for memory.

The literature lacks consensus regarding the predictive value of the Wada test with regard to postoperative memory decline. Baseline memory verbal assessment has been shown by many studies to be a particularly useful predictor of verbal memory outcome. Memory decline is more likely when ipsilateral memory is good or contralateral memory is poor (22).

Asymmetric memory performance on the Wada test may predict memory decline. Prediction of postoperative memory decline is based on concepts of functional reserve and functional adequacy. Functional reserve is linked to the integrity of the mesial temporal region contralateral to the seizure focus and represents the principal determinant of postoperative memory decline, particularly in predicting global amnesia. Evaluation of functional adequacy of the potential surgical side has greater reliability for material specific memory changes.

The most important variables that predict memory loss are baseline memory function as assessed by neuropsychological testing, the hemisphere subjected to surgery (the risk of severe amnesia exists when the language dominant hemisphere is targeted), and the existence of a structural lesion that will be removed.

## AMOBARBITAL ALTERNATIVES

Although amobarbital has been widely used to evaluate the hemispheric dominance of language and memory before temporal lobe surgery in patients with medically refractory seizures, repeated shortage of this agent has prompted many centers into using alternatives such as etomidate, propofol, sodium methohexital, or pentobarbital. Most of the published studies involve retrospective chart reviews. Intracarotid administration of 2 mg of etomidate produces a clear EEG and motor effects in all patients, with a response very similar to use of amobarbital. Shivering was the most common reported side effect (23). Methohexital, pentobarbital, and propofol have all been studied as alternatives to sodium amobarbital for the Wada test. All these required a second injection due to their short duration of action (24). There was an increased risk of seizures with methohexital use, transient respiratory depression immediately after receiving pentobarbital, and increased tone with myoclonic jerks seen with propofol use.

## REGIONAL CEREBRAL PERFUSION

The usefulness of the Wada test is limited because of inactivation of widespread hemispheric function. Therefore, selective Wada tests have been developed to deliver amobarbital exclusively in the brain portion intended to be resected. The distribution of amobarbital and its effect on regional cerebral perfusion during the Wada test using hexamethyl propyleneamine oxime (HMPAO) SPECT coregistered with patient's MRI data has been described in a pool of patients undergoing assessment for temporal lobectomy (25). The present study not only found complete mesial temporal hypoperfusion in 36% of patients, but it also found partial hypoperfusion in another 56% of patients, pointing out that the great majority of patients had some effect of the amobarbital injection on perfusion levels in the mesial temporal cortex. The lateral temporal lobe and pole showed the most perfusion, the mesial structures showed less. In mesial structures there was a variable pattern of hypoperfusion,



with some patients showing preservation of anterior perfusion and some patients showing preservation of posterior perfusion. Preservation of posterior mesial perfusion can be explained by vascular anatomy, whereas anterior preservation is more difficult to explain. Noted as well was a lack of hypoperfusion in the basal ganglia that occurred despite the fact that intracarotid HMPAO delivery and therefore amobarbital delivery was similar to other structures. This apparent resistance to amobarbital-induced hypoperfusion is postulated to be due to relative paucity of GABA<sub>A</sub> receptors that normally bind barbiturates in these structures (26).

### Anterior Cerebral Artery Wada Test

Newer techniques of inactivation of the mediobasal temporal lobe structures consist of temporary balloon occlusion distal to the origin of the anterior choroidal artery (AChA) and selective catheterization of the AChA. Only a small number of patients undergo a selective Wada test. Selection criteria included bilateral mesiobasal temporal lobe epileptogenesis, suggested by bilateral mesiobasal temporal lobe seizure onset, excessive bilateral interictal spiking, bilateral damage in structural or functional images of the temporal lobes, marked bilateral neuropsychological deficits in noninvasive neuropsychological testing, or unclear speech dominance with left-handedness. The main steps of the procedure are the introduction of a transfemoral balloon catheter, tolerance test of occlusion of the internal carotid artery by injecting contrast medium into the contralateral ICA with the compression of the ipsilateral ICA and temporary balloon occlusion distal to the origin of the AChA with injection of contrast and amobarbital. This allows for selective injection of the vascular territories of the AChA, the posterior communicating artery, and the ophthalmic artery.

The average amount of amobarbital injected with these techniques is 75 mg. As with the ICA Wada test, the patient is familiarized with the neuropsychological test procedure the day before or before the test using a similar but shorter version containing stimuli different from the real test. Continuous behavioral monitoring by videotaping the patient and synchronized EEG monitoring from scalp electrodes and preferably bilateral foramen oval electrodes are performed. Neuropsychological performances are recorded during the selective temporal lobe amobarbital test and among the three techniques: balloon techniques, superselective injection of the AChA, and the P2 segment of the posterior cerebral artery (PCA).

In comparison to preinjection performance, as expected, the postinjection performance decreases in both learning and recognition. The degree of postinjection performance depends on the type of selective amobarbital test. The left PCA selective amobarbital test has the most pronounced effect on learning and visual recognition. Verbal recognition performance decreased most with the left balloon technique. A more pronounced deficit for verbal than for visual material was seen following the left selective amobarbital

injections, and the deficit was more pronounced for visual rather than verbal material following right selective injections. The selective temporal lobe Wada tests described here mimic and predict the effects of planned selective temporal lobe surgery much better than the ICA Wada test. There is a good reported correlation between memory assessed during amobarbital injection and the actual memory outcome following surgery, suggesting that the selective Wada tests have a good predictive value for memory outcome after amygdalohippocampectomy. Given the inherent variability of the vascular anatomy of the AChA, in cases in which this artery supplies only a small portion of the anterior hippocampus, the balloon technique appears preferable to the catheterization of the AChA. In cases with a very small AChA and a small P.Comm.A. The catheterization of the P2 segment of the PCA is probably the most reliable selective temporal lobe Wada test, especially in cases in which an extensive posterior mediobasal resection is intended (27).

### Posterior Cerebral Artery Wada Test

Another procedure used by some epilepsy centers for assessing memory function is the selective injection of sodium amobarbital into the PCA. There are certain theoretical advantages of this procedure, especially the fact that the patients do not become aphasic and the drug can be delivered more effectively to the target regions, the ipsilateral hippocampus.

In this procedure, similar to the Wada test, a transfemoral catheter is used and a diagnostic angiogram is obtained in the common carotid artery ipsilateral to the proposed neurosurgical procedure, as well as in the left, right, or both vertebral arteries. The catheter is then placed in the vertebral artery and the tip is placed in the peduncular segment of the PCA with the aid of a guided wire.

With the catheter in place but before the injection the patient is presented with a list of four words read aloud. The patient is asked to recall the list of four words. At the author's center, for the memory testing procedure, amobarbital 75 mg is used to inject into the PCA. Hemianopia is used as a marker of the functional effect of the amobarbital in the PCA system. The EEG rarely shows brief bursts of theta frequency slowing in the ipsilateral posterior quadrant and is therefore an unreliable marker for the clinical efficacy of the injection. When the hemianopia is confirmed, free recall of the objects given before injection is attempted, followed by a recognition test. Immediately, a second list of six words is given with several learning trials. The hemianopia is tested every minute to assess whether the drug is still active. Hemianopia usually resolves in about 5 to 6 minutes and free recall of the second lists of words, followed by recognition test is completed. The primary assessment involves both learning and delayed recall.

Since the PCA amobarbital test does carry an increased risk of stroke and requires particular expertise in cerebral angiography, a stepwise procedure involving both the ICA

and then the PCA is usually attempted. Since the intracarotid approach involves a lower risk, it is reasonable to perform this procedure initially on all patients. If the patient fails the ICA Wada test for memory, an additional test involving the PCA approach might be considered, especially in patients with normal hippocampi or dual intrahemispheric pathology. If the patient passes the PCA Wada test, it would be reasonable to consider surgery.

### Middle Cerebral Artery Wada Test

The middle cerebral artery (MCA) Wada test involves placing the guiding catheter in the ICA below the skull base and navigating the microcatheter into the M1 segment distal to the origin of the lenticulostriate arteries or into a single MCA branch. The final catheter placement is checked by angiographic series. The MCA Wada test is performed by using the same standardized protocol that has been described for the ICA test.

The indication for the MCA Wada test is the assessment of the residual motor function before intended hemispherectomy, resection of epileptogenic lesions in or adjacent to the motor cortex or Wernicke's area, electrical status epilepticus of sleep (ESES), or partial-onset seizures with quick bilateral synchrony to the opposite side to evaluate whether ongoing bilateral epileptiform activity could be suppressed by the unilateral injection (28). In patients with developmental or early acquired hemispheric lesions involving the motor cortex, in which the functional hemispherectomy is intended, if the simple tasks (fingers flexion, thumb opposition of the thumb) are preserved, the question of disconnecting the affected motor cortex from the healthy brain without producing contralateral hand plegia cannot be answered. The type of the lesion and the timing of the insult are important parameters when predicting a patient's level of function after hemispherectomy (29). Patients with developmental lesions appear to carry a lower risk of additional motor deficits compared to patients with acquired lesions in early childhood. The prediction of postoperative deficits is most difficult in patients with relatively good motor function who had hemispheric insults perinatally and beyond the neonatal period but before completion of myelination (end of third year of life). In these cases, transcranial magnetic stimulation is difficult to perform because of distorted regional anatomy. fMRI evaluations in hemiparetic patients are often disturbed due to motion artifact.

Selective MCA Wada tests are of lesser importance in patients with acquired lesions in or adjacent to the motor cortex or the classic language areas and subdural grid electrode stimulation or fMRI are more appropriate to lateralize language functions. Although the accuracy of these investigations to detect different language representation sites within one hemisphere is yet to be determined. In patients with ESES or Landau-Kleffner syndrome, ictal epileptic discharges are usually bilateral, necessitating catheterization of the single MCA branches, usually bilaterally with higher angiographic risk.

Selective catheterization of the single MCA trunk or branches is associated with a risk of permanent neurological

deficits by inducing thromboembolic vessel occlusion or vasospasm. This risk is most likely significantly higher than with ICA Wada test. One also must be aware that even most accurate amobarbital injections do not guarantee that the drug reaches the target area. While an expected and regularly occurring contralateral hemianopia in the PCA Wada test is proof that amobarbital reached its target area, neurologic deficits are often absent in MCA Wada tests of patients with perinatal hemispheric infarcts.

In presurgical workup of epilepsy patients selective MCA Wada tests are rarely performed. The main indication is the functional inactivation of the motor cortex before functional hemispherectomy, particularly in patients with partially preserved fine motor control of the contralateral hand and finger.

The Wada test continues to be a standard investigation for determining language and memory lateralization before epilepsy surgery. However, there are shortcomings, and some patients who "fail" the Wada test still have favorable memory outcomes after temporal lobe surgery. More selective amobarbital injections into the ACA, PCA, and MCA allow more precise localization of memory functions, though they also have greater morbidity. These selective procedures may be useful in patients who fail the standard ICA Wada test.

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# Neuropsychological Evaluation

*Phillip D. Ruppert and Sarah E. Cook*

In the United States, there are approximately 200,000 new epilepsy diagnoses made each year, and approximately 3 million Americans carry a diagnosis of epilepsy at any given time. Many of these individuals experience epilepsy-related cognitive symptoms that have significant psychological, social, and economic consequences. Thus, identification and management of cognitive symptoms are important considerations in the care of individuals with epilepsy.

Neuropsychologists make distinct contributions to the interdisciplinary epilepsy care team. Neuropsychologists are clinical psychologists who have received specialized training in brain/behavior relationships, psychometric theory, psychopathology, and psychological interventions. Thus, neuropsychologists are uniquely capable of providing an objective, evidence-based assessment of an intervention for cognitive and psychological disorders in individuals with epilepsy. For these reasons, neuropsychologists are commonly consulted in the care of epilepsy patients, and the National Association of Epilepsy Centers has stated that neuropsychological services are an essential component of collaborative interdisciplinary care teams at specialized epilepsy centers.

This chapter discusses the role of neuropsychology in the care of epilepsy patients. First, we provide a brief overview of the common causes of cognitive dysfunction in epilepsy. Next, we list some of the most common referral questions posed to neuropsychologist working with epilepsy populations and describe the methods and tools used by the neuropsychologist to address these questions. Then we cover topics relevant to one of the most common reasons for referrals to neuropsychologists in epilepsy centers, evaluation of epilepsy patients for epilepsy surgery. We then turn our attention to the topic of interventions for cognitive symptoms in epilepsy patients. Finally, we briefly discuss the contributions of the neuropsychological evaluation to the identification of patients with psychogenic nonepileptic seizures.

## FACTORS CONTRIBUTING TO COGNITIVE DYSFUNCTION IN EPILEPSY

A number of factors can impact cognitive functioning in epilepsy patients. These include relatively fixed factors, such as

the nature and location of the underlying pathology causing the seizures, the age of onset for this pathology and for the seizures, and the age at which seizure treatment was initiated. Factors pertaining to the disease course are also relevant. Specifically, higher lifetime number of generalized seizures, higher number of episodes of status epilepticus, and head injuries secondary to falling during seizures are all associated with increased cognitive morbidity. Finally, more remediable or transitory factors affecting cognition include side effects of some antiepileptic drugs (AEDs), subclinical epileptiform activity, quality of sleep, recency of last seizure, and mood dysfunction.

## COMMON REFERRAL QUESTIONS

Specific reasons for referral to neuropsychology will vary for each individual case, but referral is generally made in situations where an objective assessment of cognitive and/or psychological factors will aid in the diagnosis or treatment planning for the patient. When a person with epilepsy is being considered as a candidate for palliative resection surgery, neuropsychological evaluation is often requested to obtain a cognitive baseline for comparison to postsurgical performance, to assist with the lateralization/localization of a seizure focus, and to assist in the prediction of risk for postoperative cognitive decline. In the postsurgical context, neuropsychological evaluation is commonly requested to quantify the degree of cognitive change, if any, after surgery. If postsurgical deficits are identified, results of the neuropsychological evaluation can also guide the selection of specific interventions and compensatory techniques that may help the patient to better cope with these deficits. Outside of the surgical context, the neuropsychological evaluation may be helpful for documenting areas of cognitive strengths and weakness for individuals seeking academic or occupational accommodations. In addition to questions about cognitive function, neuropsychologists are also frequently asked to provide assessment of a patient's mood, as psychiatric distress is a common comorbidity in epilepsy. Finally, neuropsychologists are occasionally asked to assist with the identification of patients who are at risk for psychogenic nonepileptic seizures.

## GENERAL ASSESSMENT STRATEGIES

An outpatient neuropsychological assessment is a relatively lengthy procedure, lasting anywhere from 3 to 8 (or more) hours. It typically begins with a detailed clinical interview where the neuropsychologist will ask the patient and family about the existing cognitive complaints. Medical, family, social, and psychiatric histories are also obtained. Based upon history obtained from records and the interview, a battery of tests is selected and administered. Many neuropsychologists have a flexible approach to assessment, meaning that they select tests based upon specific considerations for each patient rather than give the same battery to every patient. This flexible approach can be an advantage in a managed care environment where testing hours may be limited. However, there can be benefits of having a “fixed” battery for specific populations, such as in presurgical epilepsy evaluations, to promote the collection of the same variables for clinical research purposes. Depending on the setting, the neuropsychologist or a trained psychometrist will administer the tests in a standardized fashion on a one-on-one basis to the patient in a nondistracting room. Breaks are encouraged to minimize the effect of fatigue or providers may schedule testing on more than one day. Following administration, the neuropsychologist or psychometrist will score the tests using standardized criteria and each performance will be compared to established normative values. The neuropsychologist then interprets the findings and produces a report for the referral source.

### Common Tests of Specific Cognitive Domains

A typical neuropsychological assessment will measure many cognitive functions, including tests to assist in determining a patient’s level of premorbid performance and tests of intelligence. Other assessed abilities include short-term attention and working memory, speed of processing, new learning and memory, executive functioning (eg, cognitive flexibility, reasoning, problem-solving, and conceptualization), language (eg, naming, fluency, and comprehension), visuospatial and constructional skills, and fine motor skills. Mood and/or personality functioning are also frequently assessed with standardized questionnaires. Some of the tests most commonly used by neuropsychologists in the evaluation of individuals with epilepsy are discussed further. Please also refer to Table 23.1 for a brief summary of these tests.

#### *Intellectual Function*

The Wechsler Adult Intelligence Scale (WAIS), currently in its fourth edition (1), is a collection of multiple subtests that can be administered together to obtain an overall estimate of global cognitive ability, otherwise known as a Full Scale Intelligence Quotient (FSIQ). The WAIS is the most commonly used test by neuropsychologists for measuring intellectual abilities. The subtests that make up the WAIS are organized into four cognitive domains: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.

Verbal Comprehension subtests measure verbal knowledge and ability to complete verbal reasoning tasks. Perceptual Reasoning subtests measure visual-perceptual skills and ability to solve visual problems. Working Memory subtests measure auditory attention and ability to hold verbal information in short-term memory while performing mental operations on the verbal information. Processing Speed subtests measure visuo-motor speed. Sometimes an abbreviated measure of intellect is used, such as the Wechsler Abbreviated Scale of Intelligence now in the second edition (2).

#### *Achievement*

The Wide Range Achievement Test (WRAT) (3) and the Woodcock-Johnson Tests of Achievement (4) are two separate batteries of subtests that measure academic achievement, generally in the areas of reading, mathematical ability, and written expression. Administering tests of academic achievement is often helpful for identifying the presence of specific learning disorders. In persons with epilepsy, the information obtained from these measures is helpful for documenting academic strengths/weaknesses to inform possible academic accommodations.

#### *Executive Function*

*Executive function* is an umbrella term that refers to a variety of higher-level thinking skills, including attention, processing speed, working memory, reasoning, abstraction, novel problem solving, and cognitive flexibility. The following tests are some of the most commonly administered tests of executive function in a neuropsychological evaluation.

The Wisconsin Card Sorting Test (WCST) (5) presents the patient with a set of cards that he/she has to match to one of four key cards. There are rules for how the patient is to correctly match a card to the key cards, and the patient has to discern what these rules are based upon minimal feedback from the examiner. The rules for matching occasionally change, requiring the patient to adapt their matching strategy. The test measures constructs including novel problem solving, abstraction, concentration, and cognitive flexibility.

The Booklet Category Test (BCT) (6) presents the patient with successive patterns that can each be interpreted as signifying a number one through four. The patient has to use visual elements in the pattern to deduce the correct number. The answer is often not clear, but the patient is given feedback on whether each response was correct or incorrect. The test measures abstraction, visual reasoning, and ability to adapt strategy and behavior in response to environmental feedback.

The Trail Making Test (TMT) (7) requires the patient to draw a line connecting sequences of numbers and letters in order on a page. The test measures visual attention, visual scanning, processing speed, and mental flexibility.

The Stroop Color and Word Test (8) is composed of words printed in different colored ink. The printed words are actually the names of different colors, but each word is printed in a different colored ink than its name. The patient

**TABLE 23.1 Common Neuropsychological Measures by Domain**

DOMAIN	TEST NAME	DOMAINS MEASURED
Intellect	Wechsler Adult Intelligence Scale–4th Edition (WAIS-IV) (1)	General ability level
Academic Achievement	Wechsler Abbreviated Scale of Intelligence (WASI-2) (2)	General ability level in abbreviated format
	Wide Range Achievement Test–4th Edition (3)	Reading, math, and spelling achievement level
	Woodcock-Johnson Test of Achievement–3rd Edition (4)	Reading, math, spelling, written expression achievement level
Executive	Wisconsin Card Sorting Test (5)	Novel problem solving
	Trail Making Test (7)	Visual-manual scanning and sequencing speed and cognitive flexibility
	Stroop Test (8)	Speed and response inhibition
	Ruff Figural Fluency Test (9)	Novel generation of designs
	Booklet Category Test (6)	Abstraction and ability to use feedback to solve problem
	Delis-Kaplan Executive Function System (D-KEFS) (10)	Abstraction, speed of processing, working memory, novel generation of words, sequencing, cognitive flexibility, and problem solving.
Memory	Wechsler Memory Scale–4th Edition (11)	Verbal and visual memory for both rote and contextual information
	California Verbal Learning Test–2nd Edition (12)	List learning and memory
	Rey Auditory Verbal Learning Test (13)	List learning and memory
	Hopkins Verbal Learning Test-Revised (14)	List learning and memory
	Rey Complex Figure Test (15)	Visual memory
Language	Brief Visuospatial Memory Test-Revised (16)	Visual memory
	Boston Naming Test (17)	Visual confrontation naming
	Controlled Oral Word Association Test (18)	Novel generation of words starting with certain phoneme
	Semantic Fluency (19)	Generation of members of a certain category (eg, animals)
Visual-Perceptual	Judgment of Line Orientation (20)	Visual perception
	Benton Facial Recognition Test (21)	Human facial perception
	Rey Complex Figure Test (15)	Visual construction, planning, and executing complex drawing
Motor	Finger Tapping Test (22)	Fine motor speed
	Grooved Pegboard (23)	Fine motor coordination
Mood and Personality	Minnesota Multiphasic Personality Inventory–2nd Edition (24)	Psychopathology and personality
	Personality Assessment Inventory (25)	Psychopathology and personality
	Beck Depression Inventory–2nd Edition (26)	Depression symptomatology
	Beck Anxiety Inventory (27)	Anxiety symptomatology

is required to quickly state the color of ink that each word is printed in rather than reading the actual word. The test measures processing speed, cognitive control, and ability to inhibit a habitual response (reading) for a less familiar behavior (color naming).

The Ruff Figural Fluency Test (RFFT) (9) requires the patient to draw as many unique designs as possible on a

page within a limited amount of time. The test measures novel generation of visual designs and resistance to perseveration.

The Delis-Kaplan Executive Function System (D-KEFS) (10) is a battery of nine tasks designed to measure different aspects of executive function, with some subtests similar to or adaptations of the measures mentioned earlier. Some of



the executive abilities assessed by the D-KEFS include cognitive flexibility, verbal fluency, visual fluency, response inhibition, problem solving, deductive reasoning, verbal abstraction, and planning.

### *Memory*

The Wechsler Memory Scale (WMS), currently in its fourth edition (11), is a battery of multiple memory tests that primarily assesses a patient's learning and memory ability for verbal and visual information.

The California Verbal Learning Test (CVLT) (12), Rey Auditory Verbal Learning Test (RAVLT) (13), and Hopkins Verbal Learning Test (HVL) (14) are all similar tests of verbal learning and memory. These tests require the patient to learn a word list over successive trials of exposure to the list. Delayed memory for the list is tested using delayed recall and recognition tasks.

The Rey Complex Figure Test (RCFT) (15) is a test of visual memory. In this test, the patient is shown a complex figure made up of multiple, detailed visual components. The patient initially draws a copy of the figure to facilitate memory encoding. Delayed memory is tested by having the patient draw the figure from memory after a delay.

The Brief Visuospatial Memory Test (BVM) (16) is a test of visual learning and memory. The patient learns visual figures by drawing them repeatedly after successive trials of presentation of the figures. Delayed memory is tested by having the patient draw the figures from memory after a delay.

### *Language*

The Boston Naming Test (BNT) (17) is a test of confrontation naming. In this test, the patient is presented with line drawings of everyday objects and is required to give the name for each object. The test progresses in difficulty from very commonly encountered objects to objects that are less frequently encountered in daily life.

Verbal fluency tests are tasks that require the patient to generate as many words as possible that meet specified criteria under a given time limit. For example, phonemic or literal fluency requires that the patient give as many words that he/she can think of that begin with a specific letter in a minute (18). Semantic or categorical fluency requires the patient to give as many words that he/she can think of that belong to a specific semantic category (eg, tools) in a minute (19). Verbal fluency tasks measure a number of cognitive abilities, including expressive language, information retrieval from memory, executive control, selective attention/inhibition, and response generation.

### *Visual-Perceptual*

The Judgment of Line Orientation Test (JLO) (20) is a measure of visual-spatial perception and orientation. The task presents the patient with a target pair of angled lines as well as a separate semicircular array of multiple lines. The

patient is asked to tell which lines in the array match the same angle/orientation as the target pair of lines.

The Benton Facial Recognition Test (FRT) (21) is a test of visual perception and specifically assesses perception of human facial features. The test presents the patient with a picture of a target individual. The patient is then asked to identify the same individual from an array of pictures that contain both the target and the multiple foils. Foils often look similar to the target individual. Test difficulty is manipulated by varying the lighting and visual angle of target and foil faces.

### *Motor*

The Finger Tapping Test (FTT) (22) measures motor speed in the left and the right hand. The task requires the patient to rapidly and repeatedly tap a lever with his/her left and right index finger during a specified time limit. The test was designed to detect lateralized motor weakness.

The Grooved Pegboard Test (GPT) (23) primarily measures motor speed and dexterity in the left and the right hand but also can measure visual perception and fine-grained somatosensory perception. The task requires the patient to sequentially place pegs into a pegboard as quickly as possible. The pegs have a rounded side and a grooved side, so the pegs can only be placed into the board in a specific orientation. The test was designed to detect lateralized motor weakness.

### *Mood and Personality*

The Minnesota Multiphasic Personality Inventory (MMPI) (24) and Personality Assessment Inventory (PAI) (25) are self-report questionnaires measuring mood symptoms and personality characteristics. The MMPI and PAI are useful for identifying and characterizing certain Axis I and Axis II psychiatric disorders. Both tests also contain scales that measure aspects of response validity (eg, random responding, symptom over-endorsement, and symptom-minimization). Specific MMPI and PAI scales have also demonstrated mild-to-moderate usefulness in identifying individuals with psychogenic nonepileptic seizures.

The Beck Depression Inventory (BDI) (26) is a brief self-report questionnaire assessing common symptoms of depression.

The Beck Anxiety Inventory (BAI) (27) is a brief self-report questionnaire assessing common symptoms of anxiety.

## **POTENTIAL CONFOUNDS TO NEUROPSYCHOLOGICAL TEST PERFORMANCE IN EPILEPSY**

The performance of an examinee in any assessment context can be influenced by factors extraneous to a patient's actual cognitive ability. Environmental factors such as a loud noise in the clinic could momentarily distract the patient when completing a test of attention. Patient-specific factors such as fatigue, pain, decreased motivation, test-anxiety, and use of some psychotropic medications (eg, benzodiazepines) can

also affect a patient's ability to remain engaged in testing and give their best performance.

In addition to these general factors, there are factors specific to epilepsy populations that may confound test performance and interpretation. In some clinical contexts, such as a presurgical epilepsy evaluation, these factors could complicate interpretation of lateralization of the cognitive profile. One potential confound is the cognitive side effects of some AEDs. Such effects are often dose-dependent and have been shown to occur more frequently with AED polytherapy as opposed to monotherapy (28). The most common cognitive side effects of these medications are a reduction in processing speed and/or problems with attention. Therefore, any task that is timed may be negatively affected in individuals taking AEDs. For individuals with epilepsy, there is also the risk for their performance to be affected by the occurrence of a seizure during the evaluation or in the hours preceding the assessment. This is not a common occurrence but can more likely happen in individuals with a high frequency (eg, daily) of seizures. Thus, for practical purposes, parts of the evaluation may have to be completed in the context of a recent seizure. In addition to concerns about seizures and postictal confusion, test performances may be affected by subclinical epileptiform discharges. Such events last only momentarily and are often not detected by the individual with epilepsy or others around them. Such brief events could potentially interfere with test performance, particularly on tasks of attention, speed of processing or reaction time, and learning (29). To mitigate the possible effects of these confounds, efforts are made to conduct the neuropsychological testing in a comfortable, nondistracting environment (ie, a quiet room without substantial noise adjacent to it, little to no distracting room décor, the examiner conscious of their attire and hygiene, and comfortable seating). Subjective pain ratings may be taken throughout the evaluation to determine potential association with test performance. Examinees are typically given the option of taking breaks at regular intervals to reduce the possibility of fatigue, including taking breaks for meals or snacks during lengthy evaluations. Patient effort and motivation levels are often evaluated with formal or embedded tests specifically designed to detect performance validity.

If a seizure occurs during an assessment, it is customary to cease testing until the patient demonstrates resolution of any postictal confusion. While such judgments are inherently subjective and there is no consensus in the literature on how long the neuropsychologist should wait after a seizure has occurred before resuming the evaluation, common practice is to resume testing after a short period of time (eg, a few minutes) after a less severe seizure, such as a partial seizure, and to wait longer periods (eg, several hours) after more severe seizures, such as complex partial or generalized seizures. Regarding the potential for subclinical seizures to affect performance, the neuropsychological evaluation is designed to measure the same ability (eg, attention) at multiple time points throughout the evaluation, so that the effects of a subclinical event at any given time during testing is reduced in the overall summary of scores.

## ASSESSMENT OF COGNITIVE FUNCTION IN THE PRESURGICAL CONTEXT

One of the most common reasons for referral to neuropsychology in an epilepsy center is for presurgical characterization of cognitive function. Testing in this context has historically served multiple purposes, including establishment of a presurgical cognitive baseline for comparison to postsurgical function, assistance with lateralization/localization of seizure focus, and prediction of postsurgical cognitive outcomes. Literature and rationale relevant to the use of neuropsychological testing for each of these purposes is discussed in the following section. As the majority of the patients presenting for epilepsy surgery have intractable epilepsy of medial temporal lobe onset (30), the preponderance of available neuropsychological literature on presurgical evaluation is weighted toward such samples. Thus, the discussion here is focused on neuropsychological contributions to the presurgical evaluation of patients with temporal lobe epilepsy (TLE).

### Baseline Testing

Cognitive changes after surgery are common, with many patients showing measurable declines in memory or other abilities and a smaller set of patients actually showing cognitive improvements. Baseline neuropsychological testing provides unique contributions to the clinical management of surgical epilepsy patients in this context. Most importantly, neuropsychological testing allows for objective assessment of cognitive ability. As is discussed later in this chapter, patients' subjective ratings of their cognitive abilities do not always accurately reflect their actual cognitive performances. Thus, the value of neuropsychological testing is that it utilizes tests with established reliability and validity that are administered and scored using standardized procedures. Test scores can then be compared to normative samples of healthy peers that account for the effects of age and demographic factors (eg, level of education and ethnicity) on cognitive test performances. Scores can also be compared to distinct clinical populations. When baseline testing is available, a patient can serve as his/her own baseline for comparison to postsurgical performances. This can be useful for characterizing the nature of cognitive changes after surgery to inform treatment planning (eg, neuropsychological intervention) or for identifying alternative explanations for a patient's perception of cognitive change (eg, depression/anxiety). Finally, baseline and postsurgical cognitive data can be very useful for patients in making informed decisions about their academic or occupational goals.

### Localization of Seizure Focus

Certain neuropsychological tests have been shown to add incremental validity to the determination of seizure focus. Specifically, neuropsychological tests measuring verbal memory and language skills have shown the most robust sensitivity to seizure focus, with poor performance on these

measures being highly correlated with left-temporal seizure lateralization (31–38). In general, these studies indicate that poorer presurgical performances on tests of verbal memory and confrontation naming are more common in the context of left temporal seizure onset versus right. Verbal memory measures that employ a paired-associate learning paradigm (eg, Verbal Paired Associates from the Wechsler Memory Scale) are particularly sensitive to left hippocampal dysfunction. While these measures have demonstrated sensitivity to left temporal lobe dysfunction, neuropsychological markers of right temporal lobe dysfunction have been more elusive. Specifically, commonly available neuropsychological tests of visual memory have generally showed poor lateralizing value (39–43). Some have suggested that this may be due to the fact that visual stimuli can still be verbally encoded by internal verbal descriptions of what the stimuli look like.

It should be noted that much of the literature on neuropsychological lateralization of TLE assumes typical cerebral lateralization of language functioning to the left hemisphere. In fact, many of these studies attempt to control for this by excluding patients who have shown atypical language representation on Wada testing or by limiting samples to only include right-handed patients. Thus, the ability for neuropsychological testing to lateralize seizure focus is likely reduced in the context of patients who have atypical language representation or in other situations in which atypical functional organization is likely to have occurred (eg, focal left hemisphere brain injury at a very young age).

### Prediction of Risk of Memory Decline

Risk factors for postoperative memory decline have generally been conceptualized according to one of two models, termed the functional reserve model and the functional adequacy model (44). The *functional reserve* model holds that the degree of postsurgical memory decline for a given patient depends upon the capacity (ie, functional reserve) of the remaining contralateral temporal lobe to support memory function after surgery. Early support for this model came from the observations of relatively preserved memory function in most unilateral patients and profound amnesia syndromes in patients having bilateral resections or in isolated cases of unilateral resection who were later determined to have significant structural abnormality in the remaining contralateral temporal lobe (45). Additional support for the functional reserve model has come from studies using the Wada test (discussed later). Alternatively, the *functional adequacy* model holds that the functional ability of the tissue to be resected in the ipsilateral temporal lobe determines the nature and extent of memory decline after surgery. The rationale for this model is that resection of functionally intact left temporal structures will result in decline in verbal memory abilities and resection of functionally impaired structures should have minimal effect on memory. This model has received support from presurgical functional (ie, neuropsychology scores and fMRI) and structural markers (ie, hippocampal volumes on MRI). Ultimately, the risk for

postoperative memory decline is likely best determined through consideration of both ipsilateral and contralateral variables. We now provide a brief overview of some of the most commonly studied predictors of memory decline.

### Neuropsychological Testing

Multiple studies have supported the utility of presurgical neuropsychological data for estimating relative risk for postoperative memory declines. Overall, these studies have indicated that patients with higher preoperative memory scores are at a higher risk for postoperative memory decline. This effect has been most robustly demonstrated for verbal memory in patients having left temporal resections, with higher presurgical verbal memory scores indicating higher risk and greater magnitude of verbal memory decline following surgery (46–50).

### MRI

Multiple studies have shown that presurgical hippocampal volumes ipsilateral to the seizure focus are predictive of postoperative memory outcomes. Specifically, memory decline becomes less likely with increased ipsilateral medial temporal sclerosis (MTS) (50–53).

Notably, presurgical MRI and neuropsychology data are not always in perfect agreement. Specifically, there may be times when MRI shows left MTS but the patient still demonstrates intact verbal memory on testing. Predicting memory outcome in these cases is not easy. It has been suggested that verbal memory in such patients may have reorganized to be supported by the right temporal lobe, essentially reducing risk for postsurgical declines. This view has received support from the “age of onset” effect, which refers to the finding that patients with left MTS, intact verbal memory, and younger age of epilepsy onset generally have better memory outcomes after left temporal lobectomy than similar patients with more recent age of epilepsy onset. A possible explanation for the age of onset effect is that reorganization may be more likely to occur when left medial temporal damage occurs at a young age. However, this age of onset effect is not universal, and significant verbal memory decline still occasionally occurs in young onset, left MTS patients with intact verbal memory (54). In these cases, Wada testing may be informative for predicting the likelihood of memory declines.

### Wada Test

The intracarotid amobarbital procedure (IAP), or Wada test, has been used for over 50 years to determine hemispheric language dominance and risk for postoperative memory declines in temporal lobe epilepsy surgical candidates. The rationale for using the Wada test for predicting memory decline can be conceptualized in terms of the functional reserve and functional adequacy models outlined earlier. Specifically, it is thought that anesthetization of the hemisphere ipsilateral to the seizure focus can simulate resection



of those temporal structures and allow for assessment of the functional capacity of the contralateral hemisphere to support memory after surgery. Conversely, anesthetization of the hemisphere contralateral to the seizure focus allows for assessing the functional capacity of the tissue that is planned for resection. Thus, the Wada allows for independent assessment of both ipsilateral and contralateral memory function. Interpretation of the Wada for predicting memory decline typically uses the following algorithm.

- Better outcomes (eg, decreased risk for memory decline) are most likely to occur in patients demonstrating poor memory during contralateral injection and good memory during ipsilateral injection.
- Poorer outcomes (eg, increased risk for memory decline) are most likely to occur in patients demonstrating good memory during contralateral injection and poor memory during ipsilateral injection.
- For patients showing good memory during both ipsilateral and contralateral injections, there may be increased risk for verbal memory decline if resection is to occur in the language-dominant hemisphere and presurgical neuropsychological testing and MRI are also normal. Conversely, there may be increased risk for visual and/or verbal memory decline if resection is to occur in the nondominant hemisphere and presurgical neuropsychological testing and MRI are normal.
- For patients showing poor memory during both ipsilateral and contralateral injections, risk for memory decline is reduced. However, corroboration with presurgical MRI and neuropsychological testing is always recommended.

While the reasoning behind the Wada procedure makes intuitive sense, empirical documentation of its efficacy for predicting memory decline has been variable (55). This is likely partially related to the fact that the Wada procedure has never been standardized, with different epilepsy centers giving different versions of the test. A lack of standardization has made it difficult to establish basic test properties across centers, such as reliability and validity of the procedure. In addition to these weaknesses, the Wada test is an invasive procedure with increased risk of morbidity. For these reasons, use of the Wada in epilepsy centers has declined over the past decade in favor of newer, less-invasive procedures (eg, fMRI). For more information on this topic, please refer to Chapter 22 which discussed the Wada test.

### Consideration of Multiple Factors

As stated earlier, prediction of postoperative memory declines is probably best informed by consideration of multiple factors that represent the integrity of ipsilateral and contralateral structure and function. To aid the interpretation of multiple factors, some authors have published regression formulas that take into account multiple variables to assist in predicting postoperative memory performance in individual

patients (49,50). These studies have generally shown that each of the variables described earlier adds unique variance to the prediction of memory declines after epilepsy surgery.

### ASSESSMENT OF COGNITION AFTER EPILEPSY SURGERY

Postsurgical cognitive changes are typically experienced as declines relative to presurgical performance. A recent meta-analysis of outcome studies of mainly childhood-onset epilepsy found a pooled estimate of decline in verbal memory in 44% of patients with left temporal lobectomy (LTL) and in 20% of right temporal lobectomy (RTL) patients (56). Findings for visual memory were not as striking, with 21% of LTL and 23% of RTL patients experiencing decline. Naming ability is also commonly affected in left temporal resections, with declines reported in as many as 34% of cases. This study also explored subjective ratings of cognitive change postsurgery and found that self-reported declines were rather uncommon (9% of post-temporal lobectomy patients reported losses). While such estimates of change may seem concerning to someone considering TL, it is important to note that chronic epilepsy also involves a risk of cognitive decline, and from a quality-of-life standpoint, some individuals with epilepsy having postsurgical cognitive change is preferable to chronic seizures.

While declines do commonly occur, a few studies have reported improvements in select cognitive abilities in a subset of their samples (57–59). Factors that have been associated with postsurgical cognitive improvement include having a right temporal resection without structural abnormality in the remaining left temporal lobe and/or better postsurgical seizure outcome. The exact mechanisms for improved cognitive function after surgery are not fully understood, but potential explanations include a reduced seizure burden on more distal brain regions after an epileptogenic focus is resected and/or reduced use of antiepileptic drugs and their potential cognitive side effects in the context of postsurgical seizure freedom.

If there are concerns about cognitive change after surgery, reevaluation using the patient's presurgical performances as a baseline can help to objectively quantify the nature and severity of these changes. While some epilepsy services may refer all patients for reevaluation, other services may only refer individuals who have experienced significant cognitive problems postsurgically. Availability of reevaluations may be limited by a lack of referral sources to meet a high clinical volume demand. In addition, it can be a challenge getting preauthorization for reevaluations by some private insurance companies, particularly if the baseline presurgical evaluation was completed within the same year.

When conducting a follow-up assessment, neuropsychological tests can be prone to measurement error (ie, practice effects) when readministered within a short time frame. In addition, sufficient time since the surgery should have passed before reevaluation to allow for healing and

the reduction and/or elimination of pain medications. Consulting neuropsychologists may have differing opinions about how long is sufficient. Ideally, approximately 3 months postsurgery and 6 months since the baseline evaluation.

When neuropsychological reevaluations are conducted, clinical neuropsychologists may choose to use alternate forms of tests when available. Such forms have been developed and validated for several tests (eg, list-learning memory tests) shown to be particularly prone to practice effects when readministered and are considered to be equivalent to the original forms of tests. Selection of the alternate form as opposed to the standard test in reevaluation is often dependent on how much time has elapsed since the baseline evaluation. The less time that has elapsed, the more likely alternate forms will be utilized.

Once the reevaluation battery has been selected, administered, and scored, the clinical neuropsychologist is tasked with determining if there has been clinically meaningful change in cognition that can be attributable to the surgical intervention. Multiple empirically based techniques to assess change have been reported in the literature and each will be discussed briefly. More interested readers may refer to other sources for a detailed review on assessing change in neuropsychological test performance (60). The most simplistic way of assessing for change associated with surgical intervention is a discrepancy score approach (subtraction of raw preoperative from raw postoperative score). The outcome is then compared with normative data on the frequency of discrepancies in the population of interest. There are some limitations to this method, including needing the normative information for the population of interest. This method is also less precise than other methods that also account for other factors that may influence performance across evaluations.

A more sophisticated way of assessing if there has been meaningful change is by calculating the reliable change index (RCI). The clinician calculates the discrepancy in scores and then divides it by the standard error of the difference (which estimates the standard deviation of the difference scores), resulting in a z-score that can be evaluated with a normative distribution table. This method accounts for the reliability of the test, making it superior to the simple discrepancy approach.

The final way of assessing for change is by using standard regression-based equations (SRB). In this method, multiple regression is used to predict time 2 score by using the score at time 1 along with other relevant information, such as age and testing interval. It is likely the most precise measurement of change, as it takes practice effects, reliability, and test variability into account.

## INTERVENTIONS FOR PATIENTS WITH COGNITIVE SYMPTOMS

As discussed previously, a significant proportion of individuals with epilepsy experience cognitive deficits. Memory

is most commonly affected, but weaknesses in processing speed and executive functions also occur (61). These cognitive deficits often have a significant impact on daily functioning, academic/occupational functioning, and quality of life. For these reasons, many patients are interested in potential interventions for cognitive deficits. Here, we provide an overview of available behavioral and psychological interventions for cognitive deficits in epilepsy.

## Neuropsychological Interventions

The terms neuropsychological intervention or cognitive rehabilitation are commonly used to refer to psychological and behavioral interventions that are designed to promote coping and adjustment to cognitive and functional deficits through the use of compensatory strategies and residual abilities. An outline of essential factors to consider when providing neuropsychological intervention to patients with cognitive symptoms has been provided by Attix (62). These factors include assessing a patient's goals for intervention, assessing the degree of insight into cognitive symptoms, assessing the degree of motivation to participate in the intervention process, assessing the role of mood and personality factors in the patient's experience of cognitive and functional deficits, reviewing the patient's current compensatory strategies and techniques, and assessing any unique patient and environmental factors (eg, living situation and degree of support from family or friends). Intervention planning is also aided by objective neuropsychological assessment, which helps to identify and target specific cognitive weaknesses. All of these factors are important to consider when designing an individualized intervention plan for neurologic patients.

There are also general factors to consider when developing a cognitive rehabilitation program for epilepsy patients (63). Such programs should ideally provide a mix of psycho-education and teaching of specific techniques or strategies to target cognitive weaknesses. Important topics to cover in the psycho-education phase of a rehabilitation program include an overview of the nature and etiology of cognitive symptoms in epilepsy. For postsurgical patients, this may include a review of cognitive functions primarily mediated by the resected brain region (eg, naming ability in the left temporal lobe). It is also helpful to highlight the relationship between cognitive symptoms and mood symptoms, emphasizing the negative effects that depression can have on attention and self-appraisal of one's cognitive abilities. A relatively small number of studies have examined the efficacy of such intervention programs on cognitive ability in epilepsy populations, and available results have generally been positive (64–67). Together, these studies have demonstrated that relatively brief intervention programs teaching cognitive training techniques (eg, environmental adaptations, use of external aids, and teaching of mental strategies) can result in improvements on tests of learning and memory as well as significant reductions in patients' memory complaints.

## Psychiatric and Psychological Intervention

While many individuals with epilepsy experience significant problems with memory, it is important to remember that not all patients that complain of memory difficulties will demonstrate actual deficits on objective memory measures. In many cases, memory complaints are frequently more related to depression and anxiety than to actual memory dysfunction (68). This discordance between subjective memory complaints and objective memory performance highlights the importance of screening for depression and anxiety in epilepsy patients as well as the utility of a comprehensive neuropsychological evaluation for delineating cognitive and emotional contributors to memory complaints. Patients demonstrating actual deficits on objective testing may be referred for neuropsychological intervention as detailed earlier. However, for patients whose memory complaints seem to be more related to psychiatric factors, referral to a psychiatrist or a counselor would likely be more appropriate.

## Academic and Occupational Concerns

In addition to structured intervention programs, clinical neuropsychologists can be integral in assisting individuals with epilepsy regarding academic and occupational issues, including assessing for the need for accommodations at school or in the workplace, delineating which accommodations are appropriate based on an individual's own pattern of cognitive strengths and weaknesses, and educating the patient on compensatory strategies specific to such settings for cognitive weaknesses. To inform such decisions, a recent comprehensive neuropsychological evaluation has to have been completed. In some situations, and especially in the case of determining school accommodations, a neuropsychological evaluation completed as part of a presurgical evaluation may not be fully adequate for this purpose. Specifically, most presurgical evaluations do not examine school achievement skills such as reading comprehension, mathematical skills, or writing skills. Therefore, additional tests may need to be administered to best inform decisions regarding the type of accommodations being requested. Neuropsychological tests available for use at this time have not been designed to predict functioning in real-world settings such as the workplace, and therefore such tests do not always highly correlate with job performance outcomes. However, the tests available remain the most direct way to objectively assess abilities that are important in school and in the workplace.

### School Accommodations

Federal law prohibits schools from discriminating against a qualified individual on the basis of having a disability, such as a diagnosis of epilepsy. In academic settings, disability is defined as having a mental or physical impairment that substantially limits one or more major life activities. If an

individual with epilepsy meets the eligibility requirements for admission, he or she is qualified to be a student regardless of whether or not reasonable accommodations are required, even if the school believes that the disability will disqualify the student from performing the job for which they are training. When a qualified student has a disability, they have a right to reasonable accommodations, which are services or aids provided by the school to assist the student in participating in the academic program. Accommodations serve to "level the playing field" for individuals with cognitive and/or academic weaknesses. To invoke this right, the student with epilepsy needs to inform their school that they have a disability and request reasonable accommodations. Most schools have a disability services office that handles such requests. Students will likely be asked to provide documentation of the disability, such as a doctor's note. Schools reserve the right to determine which accommodations will be granted as long as it will be effective for that student. Schools have the right to refuse accommodation requests if they cause undue hardship or if the student would pose a threat to the safety of those around them on campus.

For individuals with childhood-onset epilepsy, the need for accommodations for postsecondary education may be of particular importance. In the case of absence seizures, the epilepsy syndrome may have gone unnoticed for some time, causing many lost opportunities for learning in the classroom. As noted earlier in this chapter, individuals with epilepsy are prone to other cognitive weaknesses as well, some of which may be attributable to the medications used to assist with controlling seizures. An individualized neuropsychological evaluation is necessary to determine what school-based accommodations may be helpful for an individual student's cognitive strengths and weaknesses; some example accommodations include requesting preferential seating in the classroom to reduce distractions, extra time to complete homework or exams, lecture notes provided by another student or teacher, or the ability to audiotape lectures.

### Workplace Accommodations

The Americans with Disabilities Act defines disability as a physical or mental impairment that substantially limits a major life activity. It obliges employers to provide reasonable accommodations to employees with a disability considering that the individual with epilepsy is otherwise qualified to perform the job. Reasonable accommodations allow the individual to perform the essential functions of the job and have equal employment opportunities through changes in the work environment or the way job functions are customarily done. Employers can refuse accommodation requests if it will cause undue hardship.

Employees have the burden of requesting accommodations, although some may not wish to disclose a disability during the hiring process because of the possibility of discrimination. The risks and benefits of disclosing should



be weighed if job performance is not of concern. If an employee finds that they have difficulty performing their job due to their disability, it may be best for requests to be made before disciplinary action is taken against the employee. It is up to the employer to determine what accommodations would be effective, but the employee has the right to refuse the option. In the case of a refusal, it is possible that the employee may no longer be considered qualified to perform the job. As noted earlier, a neuropsychological evaluation is helpful for determining which accommodations may best fit the employee's pattern of strengths or weaknesses; a few examples of accommodations include requesting a modified work schedule or ability to telecommute, additional training or reassignment to another position, changes to the work environment (eg, additional safety gear and lighting that does not flicker), development of checklists or calendars to compensate for memory, extra time to complete job functions, or breaking large tasks into smaller pieces to assist in maintaining attention.

### NEUROPSYCHOLOGY AND NONEPILEPTIC SEIZURE ASSESSMENT

Nonepileptic seizures are characterized by episodic change in movement, experience, or bodily sensation without EEG correlate either due to physiological (eg, syncope, migraine) or due to psychological causes. When psychological factors are considered to be the primary etiological factor, these spells are referred to as psychogenic nonepileptic seizures (PNES). While a later chapter in this volume is dedicated to PNES diagnosis and management, this brief section will detail the role of neuropsychological assessment in this subpopulation, including personality assessment, as well as research findings on cognitive performance differences between individuals with epilepsy and those with PNES.

Neuropsychologists, along with other clinical psychologists, are trained in interpreting objective personality assessments, such as the Minnesota Multiphasic Personality Inventory–2nd Edition (MMPI-2) (24) and the Personality Assessment Inventory (PAI) (25). Such inventories have shown to be useful for discriminating between individuals with epilepsy and those with PNES. Specifically, individuals with PNES are more likely to show clinically high elevations on scales suggesting somatization or conversion (69).

Research has traditionally shown that individuals with epilepsy and those with PNES perform lower than their normative peers on some neuropsychological tests. Studies examining the cognitive profiles of patients with epilepsy and those with PNES have not been able to consistently and adequately discriminate between these two groups based on objective performance alone, although some studies have suggested that patients with PNES perform worse. Several factors have been hypothesized to contribute to this,

including negative effects of mood distress and/or exaggeration of deficit in individuals with PNES (69).

There has been increasing awareness in the field of neuropsychology that the level of effort (ie, task engagement) put forth during a neuropsychological evaluation should be routinely assessed. Studies examining the rate of task effort failure have not consistently found significant differences between patients with epilepsy and those with PNES. For example, one study found effort failure in 22% of patients with epilepsy and 24% in the PNES sample (70). By contrast, Drane and colleagues found that effort failure on a more sensitive test to be present in 8% of patients with epilepsy and 51% of the PNES sample (71). They also found that when they excluded those with PNES who failed, they displayed less objective cognitive impairment on testing than those with epilepsy. In contrast, those with PNES who failed effort testing performed significantly worse than the epilepsy patients. While these findings have not been replicated in other samples (72), it suggests that it is possible that findings from previous studies where effort was not assessed may have been masked by poor performance due to poor effort on testing rather than to brain impairment.

To summarize, neuropsychologists are uniquely qualified for providing objective assessment of cognitive and psychological functioning of individuals with epilepsy. The work of neuropsychologists in this context is informed by several decades of research with epilepsy populations. Common reasons for referral to neuropsychology include presurgical characterization of cognitive strengths and weakness to inform treatment planning, postsurgical evaluation to quantify cognitive changes and inform cognitive interventions, assessment of nonsurgical patients to document cognitive deficits and inform cognitive interventions and academic/occupational interventions, and assessment of psychiatric status and risk for somatization in PNES. With specific regard to presurgical characterization, most studies have found that neuropsychological test data adds incremental validity over other presurgical data (eg, MRI and Wada) for informing treatment decisions. Finally, a practical value of neuropsychological testing in epilepsy is the information that patients can learn about their specific pattern of strengths and weaknesses and the tailored recommendations that can be provided for coping with cognitive or mood symptoms.

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# Other Techniques

*Saurabh R. Sinha*

Beyond the commonly used diagnostic modalities (eg, scalp and intracranial EEG, MRI and other imaging techniques, neuropsychological testing), there are several new/emerging techniques that may have a role in the evaluation of epilepsy. The role of these techniques remains to be fully defined. Some are routinely used at some epilepsy centers, others remain almost purely investigational. The brief summaries given here are meant purely as an introduction to the techniques and their current status with respect to clinical use.

## MAGNETOENCEPHALOGRAPHY

Magnetoencephalography (MEG) is a technique for recording the magnetic fields generated by brain activity. Whenever there is a flow of electrical current, there is an associated magnetic field that is generated. This field is perpendicular to the direction of current flow. The magnetic field is detected when it induces a small current in very sensitive, low-impedance sensors (SQUIDS or superconducting quantum interference devices). A typical MEG has 100 to 300 sensors and looks like a giant hair dryer. The patient must lie still with their head in the device for recording. Although MEG data can be reviewed in a raw format, in most instances, the MEG signal corresponding to activity of interest (eg, an epileptiform discharge or an evoked potential) is used to calculate the likely source of the activity using a model of the head.

Like EEG, activity must occur in a fairly large population of neurons with spatial and temporal summation to be detected by MEG. However, MEG is likely more sensitive, requiring only 3 to 4 cm<sup>2</sup> of activated cortex for detection of an epileptiform discharge, as compared to 6 to 10 cm<sup>2</sup> for EEG. Also, like EEG, several factors determine the appearance of cerebral activity on MEG—these include distance of source from the recording sensor and the orientation of the source (radial dipoles generate magnetic fields that are not easily detectable from the exterior surface; tangential dipoles generate fields that extend out further from the brain and are more easily detectable) (1). Owing to these factors, MEG may be more sensitive to activity in certain brain regions

than EEG and may offer additional/complimentary data to the scalp EEG. However, MEG recording is usually limited to interictal data due to the need for patients to lie fairly still in a relatively large piece of equipment. Clinical availability of such devices is also limited.

## Source Localization

For epilepsy, the main utilization of MEG has been to localize the epileptogenic zone based on interictal discharges. Analysis of MEG data provides locations of interictal discharges. These data may be more precise and more sensitive than scalp EEG. It may be particularly helpful in situations where the scalp EEG (ictal and interictal) is poorly localizing or localizes to regions not well studied with EEG, especially in nonlesional patients or patients with large or multiple potential epileptogenic lesions. For most centers, the presence of an interictal EEG discharge is essential for performing MEG. MEG data can suggest potential targets for intracranial electrode implantation and regions that may need to be included in a planned resection to optimize chances of seizure freedom.

## Functional Mapping

Another use of MEG is for mapping of eloquent cortex. By using evoked potential and functional imaging stimulation paradigms, the resulting MEG signal can be used to map regions corresponding to primary motor, primary sensory, and language cortices. Like functional MRI (fMRI) data, such data would rarely be used as the sole basis for surgery, but it can provide a starting point for localization of eloquent cortex. With advances in techniques and validation of results, a larger role in the presurgical evaluation of epilepsy and other neurosurgical patients may be possible.

## STEREO-EEG

Stereo-EEG refers to the use of multiple-depth electrodes to record intracranial EEG signals. It has long been the

avored technique for intracranial monitoring in Europe and is being used more frequently in North America. Unlike grids and strips, which can only record from the cortical surface/fissures, stereo-EEG can access deeper structures. For stereo-EEG, multiple-depth electrodes are placed through small burr holes in the skull. Planning an implantation requires some knowledge of the location of blood vessels to avoid hemorrhages. In most cases, a cerebral angiogram (conventional, CT or MR) is combined with skull and brain imaging to determine the optimal path for stereotactic placement of electrodes. Like other intracranial monitoring, placement must be planned to both allow localization of the epileptogenic zone and exclude other potential targets and eloquent cortex. In some ways, stereo-EEG requires more precise planning—unlike a grid electrode that can provide a sampling of activity over a relatively large region of cortex (tens of square centimeters), a depth electrode provides a much more localized sampling. In addition to recording spontaneous seizures and interictal activity, stereo-EEG electrodes can also be used for brain mapping using electrical stimulation. After seizure localization and brain mapping, the depth electrodes are removed. Surgical resection may be performed at this time or after a period of recovery.

There are several advantages to stereo-EEG. The biggest is easier access to deep structures like the mesial temporal lobe, orbitofrontal cortex, cingulate gyrus, and the insula. In addition, although the risk of hemorrhage during electrode placement is present, once placed, the electrodes are typically better tolerated than strips or grids. They can typically be left in place for longer periods due to the tolerability and lower infection risk. Also, it is easier to sample multiple, even bilateral, regions with stereo-EEG. In cases where surgical resection is found not to be feasible (due to multiple foci or proximity to eloquent cortex), a stereo-EEG patient has been spared a craniotomy. The main disadvantages to stereo-EEG are the limited sampling of cortex (especially for brain mapping purposes), the risk for hemorrhage during placement, the time required for placement of the many electrodes, and the relatively lack of familiarity with the procedure for most North American centers.

### HIGH-DENSITY EEG

High-density EEG (HD EEG), sometimes also called dense-array EEG, refers to the use of dense arrays of scalp electrodes (up to 256 channels or even more) to record EEGs. In most cases, such arrays are applied as part of electrode caps rather than precise measurement of locations. The electrode locations may be determined by aligning the cap with bony landmarks or by actually measuring the location of electrodes once placed. The large amount of data generated is then combined with source localization techniques to map the dipole corresponding to activity of interest. For source localization, the smaller the distance between adjacent electrodes, the higher the spatial resolution. Thus, HD

EEG can localize the source of recorded activity more precisely than conventional scalp EEG. However, noise considerations often still necessitate averaging of data (eg, multiple interictal epileptiform discharges) before source localization. Ictal EEG data may not easily lend itself to source localization techniques; instead, the raw EEG, usually with a limited number of electrodes often approximating a traditional 10-20 electrode placement, is usually reviewed. HD EEG systems can also be used for brain mapping using evoked potential techniques (2).

### NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) measures changes in blood flow based on absorption of infrared light. A fiberoptic probe is used to shine infrared light of different wavelengths (eg, 780 nm and 830 nm) onto the brain through the scalp; a light-sensitive probe is also placed on the scalp to measure the amount of reflected light. The amount of hemoglobin (and relative amount of oxygenated and deoxygenated hemoglobin) determines the amount of light absorbed at different wavelengths. Thus, the measurement can be used to detect changes in total blood flow and relative changes in oxygenation levels of hemoglobin. The point of measurement is estimated to be about 2 cm below the scalp. Multiple light sources and sensors are typically incorporated into a single device to provide spatial resolution. Thus, changes in blood flow in the superficial cortex can be measured. NIRS has been used to demonstrate changes in blood flow associated with both interictal discharges and ictal activity. Because NIRS measures changes in blood flow, the temporal resolution is low. However, there is some intriguing data to suggest that these changes may actually precede the epileptic seizure in some situations (3). NIRS also has the potential for functional brain mapping, as similar to fMRI, one can measure changes in blood flow related to certain functional tasks (motor and language).

Although discussed as a potential tool for years, NIRS is not used clinically for several reasons (4). These include limited assessment of only superficial cortical regions, significant artifacts associated with movement, limited spatial resolution, and limited temporal resolution. In addition, there has been a lack of convincing evidence that it can provide significant additional data in the evaluation of epilepsy.

### TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a noninvasive technique for stimulation of the cerebral cortex using magnetic fields. By passing a rapidly changing electrical current through a coil, a magnetic field is generated, which can then induce a current in the underlying brain tissue. By varying stimulation parameters, the underlying cortex can be studied. Such techniques have been used to show differences

in cortical excitability in patients with epilepsy and with different types of epilepsy. In addition, the technique can potentially be used as a brain mapping tool. Specifically, by measuring the precise location of the coil on the head and superimposing this on an MRI of the patient, it is possible to map out the function of specific areas, especially motor and language (5). This is a potential noninvasive tool for brain mapping before surgery, complementing data from other techniques such as fMRI. TMS also has potential applications as a means for treating seizures and other neurological/psychiatric conditions. Specifically, efficacy for treatment of refractory focal epilepsy has been demonstrated (6), although a lot more study is needed.

The techniques used in the evaluation and treatment of epilepsy are continuing to evolve. Some of the emerging techniques have already made it into clinical use and others are still at early stages of development and may never

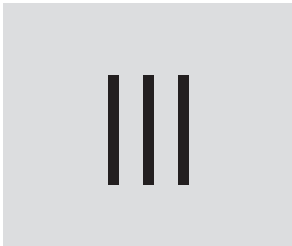
make it to the clinical arena. It is important to keep up with these changes in order to continue to improve the care provided to patients with epilepsy.

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P A R T



# Treatment





# Principles of Treatment

*Christa B. Swisher and Rodney A. Radtke*

At first glance, the medical management of a patient with seizures appears to be a straightforward process. In most settings, a patient who experiences a first seizure, accompanied by a normal brain MRI and EEG, does not warrant treatment. After a second seizure, anti-epileptic drug (AED) therapy is almost always appropriate. However, there are many factors that go into the decision to initiate AED therapy and the choice of the specific agent. These factors include lifestyle issues, psychosocial issues, acceptability of potential side effects, coadministered medications, and comorbid illnesses. In this chapter, the multiple issues that impact on the management and treatment decision in a patient with epilepsy will be addressed.

## NONPHARMACOLOGIC ADJUNCTIVE TREATMENT

### Sleep Deprivation

There are many reported precipitants of seizures. Patients with epilepsy commonly report that sleep deprivation results in worsening of their seizure control. In one survey, it was the second most common precipitant after stress (1). This was a common finding among all patients with idiopathic epilepsies, but more common in older than in younger patients. There does not appear to be a sex difference regarding the effects of sleep deprivation on seizure frequency (1). However, sleep deprivation is often associated with stress, therefore making it difficult to isolate the effect of sleep deprivation. An important component of adjunctive seizure control for all patients with epilepsy is minimizing sleep deprivation.

### Stress, Depression, and Anxiety

Epilepsy patients report that stress is the most common precipitant for their seizures (2). In addition, studies have found that there is a correlation between higher stress levels and more frequent seizures. Anxiety and depression are

frequent comorbidities in this patient population. Studies have shown that depression is significantly more common among patients with epilepsy than among the general population (2). The nature of the association between stress, depression, anxiety, and seizure control is unclear and quite complex. The mechanisms by which stress leads to increased seizure activity may be due to changes in neuroendocrine function, changes in neurotransmitter pathways, changes in gene expression, and possibly structural and functional changes in the brain (2). In addition, the presence of stress, anxiety, and depression may lead to medication noncompliance, which then can contribute to poor seizure control.

It is important for treating physicians to screen for significant life stressors and the presence of depression or anxiety. Methods of stress reduction should be discussed with the patient. If there is a concern for depression or anxiety, pharmacologic treatment or a referral to a mental health professional may be appropriate.

### Alcohol

There are little data describing the effects of alcohol on seizure frequency. The relationship between alcohol and seizures is complex because alcohol has variable effects on seizures depending on the dose and duration of alcohol use (acute or chronic use). Patients with epilepsy commonly report that alcohol use results in exacerbation of their seizures. It is difficult to determine if this is a direct effect of alcohol or secondary to sleep deprivation and medication noncompliance that can often accompany the use of alcohol. There have been no data showing that minimal or moderate alcohol use results in precipitation of seizures (3), but this has been evaluated in very few studies. Chronic, heavy alcohol use can certainly lead to alcohol withdrawal seizures. In addition, the sedating effects of many AEDs may be worsened by alcohol. Given that alcohol use is typically underreported and that seizures may be precipitated by alcohol use of any degree, neurologists should counsel all patients with epilepsy to avoid alcohol use.

FIRST AID

Principles of First Aid

Families must be educated about providing first aid during a seizure so that they can keep the patient safe until emergency medical services (EMS) arrive. The caretaker should ensure that the patient is safe from their surroundings by clearing away any objects that could injure the person during a seizure. They should not try to restrain a person who is actively seizing. The caretaker should not place any objects in the patient's mouth as this can result in unnecessary injury to the patient or the caretaker. It is recommended to gently turn the patient on their side to prevent airway obstruction and help prevent any emesis from being aspirated. Artificial respirations are rarely needed and should only be performed once the seizure has stopped and if the patient has not resumed breathing. Finally, the patient should not be given any food or water until they are completely back to their baseline mental status (4). The caretaker can administer a rectal benzodiazepine if the patient has been prescribed one and if they have been trained to do so. Oral medications should not be administered during a seizure.

When to Call Emergency Medical Services

The decision regarding when to summon emergency help for a seizure largely depends on the individual situation. EMS should be summoned for anyone suffering their first seizure. Although the seizure may be quite brief, it is important to be evaluated by a physician to possibly identify the cause of the seizure. Neuroimaging is often required to rule out an acute neurologic event, such as an intracerebral hemorrhage. In someone with a known seizure disorder, the decision to call for emergency help is usually based on a few basic rules of thumb that are outlined in Table 25.1 (4). Emergency response services should always be called if a seizure has lasted longer than 5 minutes. The observer of a seizure should be encouraged to time the seizure duration as estimates of seizure duration are almost universally overestimated due to the highly stressful situation. The vast majority of seizures last 1 to 2 minutes, and if a seizure lasts more than 5 minutes it is a situation that may become life threatening. When a seizure has lasted more than 5 minutes, the

TABLE 25.1 Indications to Call Emergency Personnel for a Seizure

If this is the individual's first seizure
If the seizure lasts more than 5 minutes
If a second seizure occurs before normal mental status returns
If there is prolonged unresponsiveness after the seizure
If an injury was sustained during the seizure
If the individual becomes aggressive after a seizure
If there is a comorbid health concern (pregnancy, diabetes)

patient is considered to be in status epilepticus and requires immediate evaluation and treatment. Additional indications for calling emergency personnel are listed in Table 25.1. EMS are most commonly summoned for a second seizure that occurs before return of normal mental status or when an injury may have occurred during the seizure.

WHEN SHOULD AN ANTIEPILEPTIC DRUG BE INITIATED?

Management of the First Seizure

*Seizure Recurrence After a First Seizure*

The most important piece of information needed when deciding if an AED needs to be initiated is knowing the risk of seizure recurrence after the first seizure. A systematic review determined that the overall risk of seizure recurrence in all age groups following the first seizure was 46% (5). There were two factors that consistently discriminated low-risk patients from high-risk patients: an abnormal EEG and the presence of a neurologic abnormality (ie, mental retardation, cerebral palsy, and neurologic deficit). A normal EEG and the absence of a neurologic abnormality placed patients in the low-risk group (24% seizure recurrence risk). The presence of an EEG abnormality and a neurologic abnormality placed patients in a high-risk group (65% seizure recurrence risk). Partial seizures appeared to be associated with an increased risk of seizure recurrence, but this finding was inconsistent across studies (5).

Based on these results, the majority of patients who present with their first seizure have less than a 50% chance of seizure recurrence, since the majority of patients will have a normal EEG and no neurologic deficits. To avoid long-term AED treatment in a large number of patients that will never have another seizure, general practice is to not initiate AED therapy after a first seizure in the absence of EEG or neurologic changes (6).

*Starting an Antiepileptic Drug After a First Seizure*

Several prospective trials have evaluated seizure risk over time after a first seizure in various patients groups. The 1-, 3-, and 5-year seizure recurrence risk for patients with either an abnormal EEG or neurologic disorder/deficit is 35%, 50% and 56%, respectively. If both an EEG abnormality and neurologic disorder/deficit are present, the 1-, 3-, and 5-year seizure recurrence risk is 59%, 67%, and 73%, respectively. In both patient groups, treatment with an AED significantly lowered these seizure recurrence risks. Therefore, it is recommended that an AED be initiated after the first seizure only if an EEG abnormality or neurologic disorder/deficit is identified (6).

Seizure Recurrence After Two or More Seizures

In adults, the overall risk of seizure recurrence after a second seizure is over 65% (5). The risk of a third seizure after having two unprovoked seizures is higher in patients with remote

symptomatic seizures when compared to patients with idiopathic or cryptogenic seizures. Interestingly, the presence of an EEG abnormality, the presence of a neurologic disorder/deficit, and seizure type were not independently associated with a higher risk of seizure recurrence in this patient population (6). A study of pediatric patients found similar results and identified a 72% recurrent seizure risk after having two unprovoked seizures (6). Given these results, it is recommended that antiepileptic medications be started in all adult or pediatric patients after two unprovoked seizures (6). There are some exceptions to this recommendation. Patients with benign rolandic epilepsy often do not require AED therapy. In addition, patients who have seizures as the result of an identified precipitant may not need AED treatment, especially if this trigger can be easily avoided. It is unclear if patients with an extremely long time period between the first and second seizures require AED therapy.

### CONSIDERATIONS WHEN DECIDING TO START TREATMENT

When a patient and physician are deciding if an AED should be initiated, there are several points to consider regarding the benefits and risks of treatment. The most important risks of ongoing recurrent seizures are death, physical injury to the patient or others, brain injury, driving restrictions, and adverse psychosocial consequences.

#### Risk of Death

There are two main causes of death specific to the epilepsy patient population: sudden unexpected death in epilepsy (SUDEP) and trauma related to seizures. Epilepsy patients have a 2.6-fold increased risk of premature death when compared to the general population. SUDEP is the most frequent cause of epilepsy-related deaths (7). The incidence of SUDEP is about 9 per 1000 patient-years in patients with refractory epilepsy (7). A single mechanism to explain SUDEP has not been identified. Potential mechanisms are arrhythmia, respiratory insufficiency, autonomic dysfunction, and cerebral dysfunction (7). It is likely that a combination of these abnormalities leads to SUDEP. Effective treatment of seizures reduces the risk for SUDEP, and this data provides strong support for the initiation of an AED after two unprovoked seizures.

#### Risk of Physical Injury

Several retrospective studies and one prospective study have evaluated the risk of injury in patients with epilepsy. The largest study of almost 1000 adults and children (>5 years old) found that patients with epilepsy have a significantly higher probability of accidents and injury than controls (27% vs. 17%) (8). Although many of the injuries in this patient population are minor, more concerning injuries including submersion injury, burns, fractures, head injuries, motor vehicle accidents, dental trauma, and soft

tissue injury do occur. Submersion injury, which is associated with a high mortality, is 7.5 to 13.9-fold higher in the pediatric epilepsy patient population when compared with age-matched controls (8). The risk of fracture in adults and children is elevated twofold (8). This is discussed in more detail in Chapter 36, Bone Health. The risk of motor vehicle accidents is only slightly higher in epilepsy patients when compared with controls but limited difference is likely in part due to the driving restrictions placed on patients with uncontrolled seizures (8).

### Risk of Neuronal Damage

Numerous animal and human studies have found an association between recurrent seizures and neuronal injury, although direct causality has not been established. Findings in humans that support the hypothesis of seizure-induced neuronal damage include hippocampal neuronal loss, elevation in makers of neuronal injury, cognitive and memory decline, behavioral problems in children, hippocampal atrophy, and cerebral and cerebellar volume loss (9). While individual seizures are not likely to result in any evident neuronal injury, the cumulative effects of uncontrolled seizures can be identified in many patients over time.

### Psychosocial Consequences of Epilepsy

There are numerous psychosocial difficulties that affect children and adults with epilepsy. Although treatment with AEDs does not definitively reduce the risk of these issues, consideration of these factors may be important when deciding whether to initiate treatment. It should be noted that some of these psychosocial difficulties are directly related to side-effects of the AEDs themselves. The most frequently encountered psychosocial difficulties in patients with epilepsy are stigma, loss of control, depression, memory deficits, reduced quality of life, anxiety, cognitive deficits, and emotional problems. Inability to drive often adds to a sense of loss of control and often compromises employment opportunities.

### DECIDING WHICH ANTIEPILEPTIC MEDICATION TO INITIATE

Once it has been decided that AED therapy will be initiated, there are many factors to take into consideration for AED selection. There are numerous AEDs to choose from, and AED selection should be tailored to each individual patient. Many new AEDs have been approved by the FDA, making this selection process even more complex. A list of factors to consider during AED selection is shown in Table 25.2.

The type of epileptic disorder will play a large role in determining the type of AEDs selected. There is never one sole AED indicated for a certain type of epileptic disorder. However, there are some general recommendations to help guide the selection process. Some AEDs have been found to only be effective in the treatment of partial-onset seizures.



**TABLE 25.2 Factors Affecting AED Selection**

MEDICATION-RELATED	PATIENT-RELATED
<ul style="list-style-type: none"> <li>■ Potential side effects</li> <li>■ Potential drug–drug interactions</li> <li>■ Safety</li> <li>■ Frequency of administration</li> <li>■ Need for titration</li> <li>■ Available formulations (tablet, liquid, IV)</li> <li>■ Cost and availability</li> <li>■ Mechanism of action</li> <li>■ Requirement for blood monitoring</li> <li>■ Approved indications</li> </ul>	<ul style="list-style-type: none"> <li>■ Seizure type</li> <li>■ Epilepsy syndrome</li> <li>■ Age</li> <li>■ Gender</li> <li>■ Potential reproductive issues</li> <li>■ Medical comorbidities</li> <li>■ Patient acceptance of specific side effects</li> </ul>

Other AEDs are felt to have broad-spectrum efficacy against both partial-onset and generalized epilepsy. Other factors to take into consideration with initial AED selection are medication safety, cost, patient preferences, side effects, ease of use, and possible interactions with other medications.

Providing a patient with a feasible dosing regimen for their lifestyle is very important. Most AEDs can be administered daily or twice a day. It is very difficult for patients to consistently remember to take medications during the day and dosing regimens of three times a day should be avoided if possible. There are several long-acting formulations for various AEDs, and these can be helpful in improving medication compliance in some patients. Dose titration of AEDs may be quite lengthy and complex at times, which complicates the management of many patients. It is essential that the patient receive clear and simple instructions regarding dose titration. Patients should be educated as to what to do if they miss a dose of their medication. Use of a weekly pill box should be encouraged as it helps improve compliance and allows easier identification of any missed medication.

### Medication Safety

Serious, idiosyncratic reactions can be seen with several AEDs. Felbamate has been associated with a risk of aplastic anemia and liver failure. Irreversible retinopathy has been reported with vigabatrin, resulting in a concentric visual field defect. Liver failure is seen infrequently with valproate use (1 in 20,000–100,000). This risk increases in children less than 2 years old, patients receiving AED polytherapy and patients with developmental delay (10). A risk of Stevens-Johnson syndrome is associated with carbamazepine and lamotrigine. The risk of this serious side effect is increased in patients with the HLA allele, HLA-B\*1502. Since this allele is present almost exclusively in patients of Asian descent, it is recommended that Asian patients be screened for this allele before initiation of carbamazepine (10).

One of the primary issues pertaining to drug safety is the risk of teratogenic side effects. Women of child-bearing age require special attention when choosing an AED

regimen. Women with epilepsy taking AEDs have a two-fold risk of having a baby with a major birth malformation, when compared to healthy women taking no medications (2% to 4%) (11). The incidence of major congenital malformations (MCM) related to each AED varies across studies, but the AED that appears to have the highest risk is valproate with some studies citing a risk as high as 10.7%. Phenobarbital also appears to have a significant risk of MCM but to a lesser extent than valproate (11). Carbamazepine and valproate are believed to have an increased risk of neural tube defects when compared to other AEDs (11). With the increasing information becoming available from the various pregnancy registries, lamotrigine and levetiracetam are perceived as having the lowest incidence of teratogenic side effects. This topic is discussed more extensively in Chapter 35, Reproductive Issues.

### Medication Tolerability and Side Effects

All medications have potential side effects, and this is especially true for AEDs. It is essential to take these potential side effects into consideration when selecting an AED. If a patient does not tolerate their medication, compliance will be problematic and likely result in worse seizure control. Most AEDs have a potential side effect of drowsiness and cognitive complaints, but some AEDs tend to cause this side effect more often than others (see Table 25.3). The acceptability of such side effects may differ between patient populations. For example, a young patient in college may have a much lower threshold for tolerating drowsiness and cognitive slowing than an older patient involved in manual labor.

At times, side effects can be used to a patient's benefit and to positively affect other medical conditions. Patients with difficulty sleeping may actually benefit from a medication with drowsiness as a frequent side effect. Change in weight is also a common concern. Topiramate and zonisamide may be helpful in an obese patient desiring weight loss, but should be avoided in patients with anorexia nervosa. Valproate and pregabalin frequently contribute to weight gain. Gabapentin and pregabalin may be helpful in patients with painful peripheral neuropathy. Valproate

TABLE 25.3 Cognitive Side Effects of Various AEDs

FREQUENT COGNITIVE SIDE EFFECTS	VARIABLE COGNITIVE SIDE EFFECTS	MINIMAL COGNITIVE SIDE EFFECTS
Topiramate	Phenytoin	Levetiracetam
Primidone	Carbamazepine	Lacosamide
Phenobarbital	Valproate	Gabapentin
	Zonisamide	Pregabalin
		Lamotrigine

and topiramate have been FDA approved for the treatment of migraines. In addition, other AEDs such as zonisamide, lamotrigine, pregabalin, and gabapentin are often used off-label in the prophylactic treatment of migraines and can be used to target both seizures and migraines together.

The presence of coexisting psychiatric problems can help determine AED selection. Some AEDs (levetiracetam, phenobarbital, zonisamide, and topiramate) are associated with an increased risk of depression and should be avoided in patients with known major depressive disorder as it may exacerbate their symptoms. Conversely, some AEDs (lamotrigine, valproate, carbamazepine, and oxcarbazepine) can have a beneficial effect on mood or act as a mood stabilizer. These AEDs can be helpful in epilepsy patients with coexisting bipolar disorder.

Some AEDs may have specific adverse side effects in women. Valproate should be avoided in younger women, because use of this AED may increase the incidence of polycystic ovarian syndrome (PCOS). PCOS presents with anovulation and hyperandrogenism (acne, hirsutism, and male-pattern hair loss). In addition, weight gain and hair loss are potential side effects of valproate, making this a particularly unappealing medication in adolescent and young adult women.

## Possible Interactions With Other Medications

It is essential to review a patient's medication list before initiation of a new AED to avoid drug–drug interactions. Although these possible interactions are too numerous to discuss, a few of the most commonly encountered situations will be discussed.

Enzyme-inducing AEDs can have adverse consequences when coadministered with other medications that are hepatically metabolized (11). Figure 25.1 depicts the interactions between AEDs and the hepatic P450 enzyme system. The most serious and commonly encountered medication interaction is with warfarin. The interaction between warfarin and enzyme-inducing AEDs is quite complex. Carbamazepine enhances the metabolism of warfarin, requiring higher doses of warfarin when coadministered with carbamazepine. The interaction between phenytoin and warfarin is more complex. Initially, phenytoin appears to enhance the anticoagulation effect of warfarin, however after several weeks of therapy the opposite effect is seen. Clinically, this translates into widely fluctuating international normalized ratios (INR), and extremely close INR monitoring is needed in these situations.

Enzyme-inducing medications enhance the metabolism of estrogen and progesterone, leading to a reduced efficacy of oral contraceptives (11). This effect can potentially be seen with phenytoin, primidone, phenobarbital, carbamazepine, oxcarbazepine, and topiramate (11,12). These AEDs induce the hepatic CYP 3A4 isoenzyme, which is involved in the metabolism of oral contraceptives. A different type of interaction is seen between lamotrigine and oral contraceptives. Oral contraceptives increase the clearance of glucuronidated drugs, and lamotrigine is hepatically metabolized by glucuronic acid conjugation. Estrogen exposure results in a marked reduction in lamotrigine levels and may affect seizure control. Further discussion about these topics can be seen in Chapter 35, Reproductive Issues.

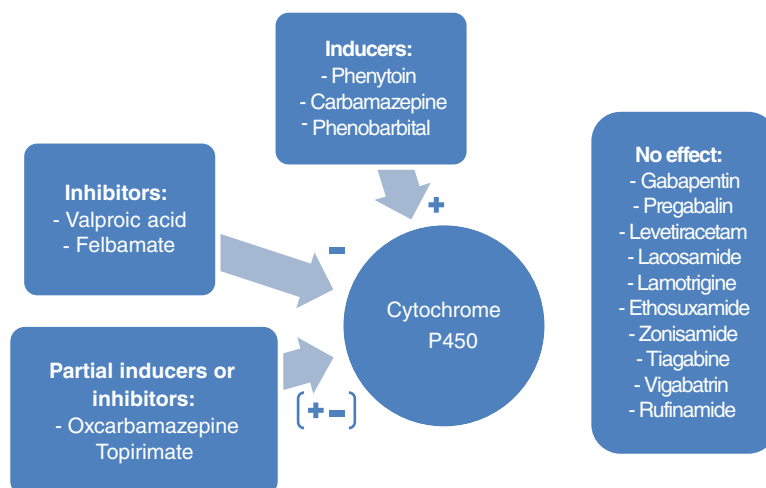


FIGURE 25.1 Interactions between AEDs and cytochrome P450.

Many patients with brain tumors develop epilepsy and require treatment with AEDs. Certain AEDs may affect the metabolism of chemotherapeutic drugs, resulting in either toxicity or loss of efficacy of the chemotherapeutic drug (13). Studies have shown that enzyme-inducing AEDs enhance the metabolism of certain chemotherapeutic drugs. Similarly, some chemotherapeutic drugs can affect the metabolism of phenytoin and valproic acid. Newer, non-enzyme-inducing AEDs are preferred when a patient is also receiving chemotherapy (13).

Antiepileptic Drug Selection by Seizure Type

The type of seizure and the epilepsy syndrome typically guide AED selection. The vast majority of AEDs are considered effective for focal-onset seizures, with the exception of ethosuxamide. For primarily generalized seizures, there are fewer AEDs that have been shown to be effective. A brief discussion regarding seizure type and AED selection will follow, but more detailed discussion of the various AEDs is presented in Chapters 26 to 29. AEDs are considered to be either narrow spectrum or broad spectrum (Table 25.4). Narrow-spectrum AEDs are effective for partial seizures with or without secondary generalization, somewhat effective for primary generalized tonic-clonic seizures, and either worsen or are ineffective for myoclonic or absence seizures (11). Broad-spectrum AEDs have been shown to be effective in both partial seizures and primary generalized seizures. Although the FDA indication for both lacosamide and perampanel is in partial epilepsy, there is some initial experience suggesting that they may be effective in primary generalized epilepsy as well. If the type of epilepsy is unknown, it is suggested that a broad-spectrum AED be used. A broad-spectrum AED will often be used in pediatric patients as many more patients present with primary generalized epilepsy. Conversely, older adults with new-onset seizures almost always have localization-related epilepsy, making narrow-spectrum AEDs a reasonable option in this age group.

TABLE 25.4 AED Spectrum of Activity

NARROW-SPECTRUM AEDS	BROAD-SPECTRUM AEDS
Carbamazepine	Valproate
Oxcarbazepine	Levetiracetam
Gabapentin	Lamotrigine
Phenobarbital	Topiramate
Phenytoin	Rufinamide
Lacosamide (? broad spectrum)	Zonisamide
Pregabalin	Clobazam
Primidone	
Tiagabine	
Ezogabine	
Perampanel (? broad spectrum)	

COMBINATION ANTIEPILEPTIC THERAPY

AED monotherapy provides optimal seizure control in about 60% to 70% of patients. The usual approach is to initiate a single AED and titrate up until seizure control is achieved or side effects are identified. AED levels are used to help guide dosing with several of the AEDs. However, the main goal is to achieve seizure freedom in the absence of side effects. If the first monotherapy is inadequate, a second monotherapy trial is usually attempted. If the second monotherapy trial is also ineffective, most neurologists would consider combination therapy as the next step. However, if the AED trials were failures due to unacceptable side effects, additional monotherapy trials would likely be pursued. Although the addition of a second, third, or possibly fourth AED may be beneficial in terms of seizure control, the risk of adverse side effects also increases substantially.

With over 20 AEDs available, there are 200 possible dual-AED combinations and over 1000 possible triple-AED combinations. Therefore, it can be difficult to decide which AED combination to utilize for each patient. Many epileptologists prefer to use AEDs with different mechanisms of action. Table 25.5 lists the various mechanisms of action for many of the AEDs. In theory, this provides broader antiepileptic effects that hopefully increase the likelihood of seizure control. This is the basis for the concept of “rational polytherapy” and is supported by animal data showing that efficacy is improved when AEDs with different mechanisms of action are used (14). The most successful combination in animal models has been combining a single-mechanism AED with an AED that has multiple mechanisms of action (14). Strengthening the antiepileptic pathway of one AED by adding another AED with the same mechanism of action has been shown in animal models to be least effective. Moreover, combining sodium channel-blocking AEDs (phenytoin, carbamazepine) is likely to cause intolerable side effects such as diplopia, dizziness, and ataxia. Of note, lacosamide in combination with phenytoin or carbamazepine appears to be effective, possibly because lacosamide acts on slow inactivation of sodium channels, while phenytoin and carbamazepine act on fast inactivation of sodium channels (14). However, the typical “sodium channel” side effects of dizziness and diplopia are more common when using lacosamide with one of the traditional sodium channel drugs. In addition to the drugs listed in Table 25.5, two new agents with unique mechanisms of action have recently become available and are FDA approved for the treatment of partial seizures. Ezogabine enhances function of the potassium channel, while perampanel serves as an AMPA receptor antagonist. What potential clinical role these drugs with unique mechanisms of action will have remains to be determined.

Unfortunately, there is little clinical data to guide the process of selection for AED polytherapy. Many epileptologists perceive the presence of synergistic efficacy with the combination of valproate and lamotrigine, and there are at least some data in the literature to support that observation



TABLE 25.5 AED Mechanisms of Action

SODIUM CHANNEL BLOCKERS	CALCIUM CHANNEL BLOCKERS	GABAERGIC AEDS	MULTIPLE MECHANISMS OF ACTION OR UNKNOWN
Fast inactivation: – Phenytoin – Carbamazepine – Lamotrigine – Oxcarbamazepine	Ethosuxamide Gabapentin Pregabalin	Barbiturates Benzodiazepines Vigabatrin Tiagabine	Levetiracetam Valproate Felbamate Topiramate Zonisamide Rufinamide
Slow inactivation: – Lacosamide			

(14). Other successful or preferred AED combinations have been reported in small case series or case reports; however, there is no substantial evidence to guide clinical practice.

### WHEN SHOULD ANTIEPILEPTIC DRUGS BE DISCONTINUED?

Approximately two-thirds of patients will become seizure free when treated with AEDs. An important concern for both physicians and patients is the possibility of successfully discontinuing AED therapy. Consideration of AED withdrawal in a patient who has been seizure free on AEDs can be a difficult decision. An in-depth conversation must be held with the patient regarding the pros and cons of AED withdrawal. Patient-related factors can play a large role in this decision. In adults, seizure recurrence can equate to loss of a drivers license and loss of employment. A patient's occupation may play a significant role in the decision process, especially if they have a risky occupation that would result in injury to themselves or injury to others if a recurrent seizure were to occur. On the other hand, patients may have a strong desire to discontinue AEDs in hopes of no longer experiencing the effects of chronic medication use (side effects, stigma, and psychological effects).

A meta-analysis showed that the overall rate of seizure recurrence after AED withdrawal is 25% at 1 year after discontinuation and 29% at 2 years. However, it should be noted that the annual relapse rate for patients on AEDs who have been seizure free for 2 years is about 8%. The majority of seizure relapses occurred within the first 12 months after discontinuation of therapy. Factors associated with a higher risk of seizure relapse after AED discontinuation are age greater than 16, abnormal EEG, seizures upon awakening, myoclonic seizures, AED polytherapy, history of breakthrough seizures after the initiation of AEDs, the presence of juvenile myoclonic epilepsy, the presence of mental retardation, abnormal neurological exam, and hippocampal sclerosis on MRI (15). Although there are no specific guidelines suggesting how AED discontinuation should be managed in patients with these characteristics, the patient needs to understand that there is a substantial risk of recurrence if they are in these high-risk groups.

The timing of initiation of AED withdrawal has been studied. A Cochrane review supported waiting for at least 2 years of seizure freedom in pediatric patients before attempting AED withdrawal. Studies have shown that there is a higher risk of seizure relapse with a shorter duration of seizure freedom. The data for adult patients are not as clear. However, common practice is to wait until adult patients are also at least 2 years seizure free before the initiation of AED withdrawal (15).

The ideal speed at which AEDs should be withdrawn is unknown. A Cochrane review was unable to determine the optimal rate of AED weaning. Studies have found no difference in seizure relapse rates between short tapers (6 weeks) and long tapers (9 months) (15). However, there are some general principles to guide practice. AEDs with longer half-lives are tapered more slowly to avoid withdrawal seizures. Patients on higher doses of AEDs will likely need longer periods of tapering. In general, most epilepsy specialists prefer to taper AEDs slowly as a precaution. Epilepsy is a chronic condition and rarely there are abrupt or rapid changes in AED therapy warranted in the outpatient management of epilepsy.

### SPECIAL TREATMENT PRINCIPLES IN VARIOUS AGE GROUPS

#### Elderly Patients

New-onset epilepsy in elderly patients tends to be localization related, making narrow-spectrum AEDs a reasonable choice in this patient population. However, epilepsy in the elderly is usually more readily controlled and so the major issues in AED selection are avoidance of side effects or bothersome drug-drug interactions. Dizziness and gait instability are AED side effects seen in all age groups, but elderly patients are more susceptible to these particular side effects. Medications such as phenytoin, carbamazepine, and oxcarbamazepine should be avoided in elderly patients due to the high risk of falls associated with these medications (11). These same older enzyme-inducing agents are all also the drugs that are likely to have bothersome drug-drug interactions.

### Pediatric Patients

Aside from proper selection of an AED based on the seizure type, there are several additional considerations in the pediatric patient population. These include tolerability, side effects, and potential for medication interactions. One main concern in pediatric patients has been the effect of AEDs on cognition. Although the evidence is inconclusive, the literature suggests that older AEDs have a detrimental effect on cognition (16). There are little data evaluating the cognitive side effects of newer-generation AEDs. An increased incidence of behavioral side effects of AEDs have been seen with several agents, with the incidence being highest with levetiracetam and phenobarbital.

## SPECIAL TREATMENT PRINCIPLES IN VARIOUS MEDICAL CONDITIONS

### Liver Failure

Managing patients with epilepsy and liver disease can be difficult because almost all AEDs undergo hepatic transformation, except for gabapentin and vigabatrin. Levetiracetam, topiramate, lacosamide, and zonisamide are only partially hepatically metabolized. The rest of the AEDs are predominantly metabolized by the liver. Liver dysfunction can affect the metabolism of AEDs at several different points during the hepatic metabolism pathway. This can lead to the accumulation of AEDs or impair the process of metabolite production. In addition, the presence of some AEDs may lead to worsening of the underlying hepatic injury.

Markers of hepatic injury are elevated serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALK PHOS), ammonia and an abnormal coagulation profile. Valproate has been shown to elevate serum ammonia levels independent of liver function. This elevation in ammonia can be two- to threefolds and is usually clinically insignificant. Although mild elevations in hepatic enzymes can be seen with AED therapy, elevations in hepatic enzymes more than two- to threefolds should alert the clinician to potential liver injury. Liver disease induced by AEDs can be part of a generalized hypersensitivity reaction. Concomitant symptoms include rash, eosinophilia, and lymphadenopathy. A significant elevation in hepatic enzymes may be sufficient cause to switch to a different AED. Dose-dependent hepatotoxicity is rare, but when it does occur, it is typically reversible when the AED is stopped.

Due to hepatic metabolism, the dose of benzodiazepines, lamotrigine, and topiramate should be reduced in patients with liver disease. Carbamazepine will cause a brief, asymptomatic elevation in hepatic enzymes in 25% to 61% of patients. Severe hepatotoxic reactions to carbamazepine tend to occur within 3 to 4 weeks of initiation and are often reversible if discontinued, but fatal hepatotoxicity can occur. Hepatotoxicity has not been reported with ethosuxamide or zonisamide use. Serious hepatotoxicity has been

reported with felbamate. There have been rare reports of liver disease related to lamotrigine, oxcarbamazepine, and topiramate use. Phenobarbital can cause an asymptomatic elevation in AST and ALT, a dose-dependent hepatotoxicity or a serious idiosyncratic reaction. The majority of patients taking phenytoin will have an elevation in GGT and alkaline phosphatase and usually do not result in a change in therapy. A few patients on phenytoin will have an elevation in AST and ALT, but these increases in liver enzymes are typically asymptomatic. A serious hypersensitivity reaction rarely occurs with phenytoin, but its use does carry a 10% to 38% mortality rate. Valproate can cause an asymptomatic elevation in liver enzymes. If the patient is asymptomatic, then changing to another AED is necessary only if there is at least a two- to threefold elevation in liver enzymes. Valproate can also rarely cause a fatal, irreversible hepatic injury in the first 2 to 3 months of therapy, particularly in children receiving polytherapy who are less than 2 years of age. Valproate should not be used in patients with known liver disease (17).

### Renal Failure

The majority of newer AEDs undergo renal metabolism. This section will discuss general characteristics of AEDs in the setting of renal disease. Dose adjustment is not needed in patients with kidney disease taking phenytoin, carbamazepine, valproate, ethosuxamide, or tiagabine. Conversely, dose adjustment is needed in patients with kidney disease taking phenobarbital, primidone, gabapentin, levetiracetam, topiramate, oxcarbamazepine, felbamate, or lacosamide.

Renal disease may result in reduced protein binding of phenytoin and subsequently higher levels of free phenytoin. Therefore, monitoring of free levels of phenytoin is recommended in patients with renal disease. There have been rare reports of interstitial nephritis associated with phenytoin, carbamazepine, valproate, phenobarbital, or lamotrigine use. Ethosuxamide can cause a drug-related systemic lupus erythematosus, which may include renal involvement. Topiramate can cause nephrolithiasis and metabolic acidosis. Similarly, zonisamide can cause a renal tubular acidosis and nephrolithiasis. About 35% of zonisamide is excreted unchanged in the urine and probably does not require dose adjustment in the setting of kidney disease, but this has not been well studied. Lamotrigine is metabolized in the liver into an inactive metabolite, which is then excreted in the urine; therefore, dose adjustment in the setting of renal disease is probably not necessary. However, there are reports of altered pharmacokinetics of lamotrigine in patients with renal disease, and caution is recommended in patients with a glomerular filtration rate (GFR) less than 15 ml/min (18).

## FDA LABELING FOR ANTIEPILEPTIC DRUGS

In 2008, the U.S. Food and Drug Administration (FDA) issued a warning for the increased risk of suicidal thoughts

and behaviors for all AEDs. This decision was based on an FDA review of 199 clinical trials that evaluated the use of 11 AEDs. The FDA determined that patients receiving AEDs have double the risk of suicidal behavior or thoughts (0.43%) when compared to patients receiving placebo (0.24%). Overall, there were four patients who committed suicide who were randomized to receive an AED and none in patients who were randomized to receive a placebo. The FDA stated that the reasons for this apparent increased risk were unknown. In the FDA analysis, AEDs were prescribed for epilepsy in 25%, psychiatric illness in 27%, and for other indications in 48%. The odds ratio for the association between suicidal thoughts and behavior was 1.8 (95% CI 1.24–2.66). The odds ratio was not statistically significantly elevated for suicidal thoughts alone (19).

Despite this labeling by the FDA, the general consensus among neurologists is that the risks associated with discontinuation of AED treatment or withholding AED treatment in patients with epilepsy far outweigh the risk of suicide. Specifically, this refers to the risks of accidents and of SUDEP in patients with poorly controlled epilepsy. Many neurologists feel methodological concerns were present in the FDA study and that the labeling was excessive and applied too broadly. There is a concern that AEDs were unjustly grouped together in this warning, despite the likely differences among individual AEDs with their markedly different mechanisms of action and side effect profiles (20).

### OTHER MEDICATIONS THAT MAY INCREASE THE RISK OF SEIZURES

Numerous classes of medications have been shown to cause drug-induced seizures or to lower the seizure threshold in patients with epilepsy. A list of medications commonly reported to have proconvulsant effects is shown in Table 25.6. Whenever a patient presents with their first seizure, it is important to review their medication list to identify any medication that may have potentially caused the seizure, especially if the medication was recently initiated. An estimated 6% to 9% of first-time seizures are thought to be related to medication. Drug-induced seizures may also present as status epilepticus. Medication-related seizures can occur in the setting of appropriate dosing, toxicity, or

withdrawal. Withdrawal seizures are most commonly seen with benzodiazepines, baclofen, alcohol, and barbiturates. The most common medications that result in new-onset seizures or worsening of seizures in patients with epilepsy are antibiotics, stimulants, antidepressants, and antipsychotics.

When evaluating a patient with new-onset seizures, there are many things to consider regarding treatment. There are nonpharmacologic treatment options that should be discussed with all patients. Based on the history, examination, and investigations, the decision to start or withhold AED treatment will need to be made. Once the decision to prescribe an AED is made, the selection of the best one involves several considerations. A thorough understanding of the various AEDs available, their indications, adverse effects, drug–drug interactions, and effects in special populations must be evaluated. Most people with epilepsy can be successfully treated with AEDs and sometimes the medications may even be withdrawn after years of seizure control.

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**TABLE 25.6 Medications That may Cause Seizures**

Antibiotics	Narcotic and nonnarcotic analgesics
– especially ciprofloxacin, levofloxacin, imipenem-cilastin, cefepime, ceftazidime	– meperidine and tramadol
Antipsychotics	Respiratory agents
– highest risk with clozapine	– theophylline, isoniazid
Antidepressants	Drugs of abuse:
– highest risk with bupropion, tricyclic overdose	– cocaine, ecstasy, MDMA, PCP
Stimulants (amphetamine type)	Anticholinergic/antihistamine drugs

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# First-Generation Antiepileptic Drugs

*José E. Cavazos*

## 26

### CHAPTER

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The first-generation antiepileptic drugs (AEDs), often known as traditional AEDs, marked a significant advance in epilepsy therapy. Before the introduction of phenobarbital, epilepsy was treated with bromide and various faith-based treatments. Subsequent discovery of drugs such as phenytoin, carbamazepine, valproic acid, ethosuximide, and benzodiazepines provided other treatment options. These AEDs will be discussed in more detail in the present chapter. A summary of their properties is presented in Table 26.1 (located at the end of the chapter).

#### BENZODIAZEPINES

##### Indications

In this section, the benzodiazepines clonazepam, diazepam, and lorazepam will be discussed as they are used most often in the treatment of epilepsy. Benzodiazepines are recommended for the adjunctive treatment of convulsive disorders, particularly during clusters of seizures. Clonazepam has a longer half-life than diazepam and lorazepam, and it has been found useful as adjunctive therapy for Lennox-Gastaut syndrome, akinetic and myoclonic seizures. Clonazepam might also be useful in patients with absence seizures who have failed to respond to ethosuximide. Intravenous diazepam and lorazepam are also indicated for the acute treatment of status epilepticus. Although status epilepticus is defined as continuous seizures for over 30 minutes, in practice, diazepam and lorazepam are used as first-line agents once seizures last longer than 5 minutes.

##### Dosing

Diazepam is recommended for the adjunctive treatment of convulsive disorders with usual dose of 2 to 10 mg orally twice to four times per day. The gel rectal delivery system for diazepam (Diatat) is a nonsterile, slightly yellow gel provided in a prefilled, unit-dose, rectal delivery system and contains diazepam at the concentration of 5 mg/ml. Diazepam and lorazepam are also available for intravenous dosing

of 1 to 5 mg. In addition, lorazepam can be administered intramuscularly, with complete and rapid absorption reaching peak concentrations within 3 hours. Clonazepam is available in tablets ranging from 0.125 mg to 2 mg.

##### Pharmacology

The likely mechanism of action of benzodiazepines is the interaction with gamma-aminobutyric acid (GABA) receptors of the A-type (GABA<sub>A</sub>), resulting in an increased frequency of chloride channel openings, making it harder for neurons to depolarize. Diazepam oral or rectal is easily absorbed reaching peak plasma concentration in 1 to 1.5 hours (range of 0.25–2.5 hours) and has a bioavailability greater than 90%. Its oral absorption is delayed when coadministered with a meal high in fat. Diazepam binds extensively to plasma proteins (95%–98%) and is metabolized by CYP2C19 (Cytochrome P450 2C19) and CYP3A4 (Cytochrome P450 3A4) to an active metabolite, desmethyldiazepam. Diazepam and its active metabolite easily cross the blood–brain and placenta barriers. In normal healthy adults, the elimination half-life is 46 hours and for its active metabolite is 71 hours. Lorazepam has similar peak concentrations to diazepam, but it has a faster half-life of about 14±5 hours after a parenteral administration. Lorazepam is also strongly bound to plasma proteins (89% to 93%). Lorazepam is metabolized by hepatic glucuronidation. Lorazepam penetrates the blood–brain barrier freely by passive diffusion, and it is the agent of choice for status epilepticus. Clonazepam has peak concentrations in 1 to 4 hours after oral intake with bioavailability exceeding 90%. Its elimination half-life is typically 30 to 40 hours. Clonazepam undergoes metabolism by the CYP3A family.

##### Efficacy Data

Diazepam may be used as an adjunctive treatment in convulsive disorders as it has not proven useful as a sole therapy. Some practitioners utilize benzodiazepines for the adjunctive treatment of clusters of seizures. There are several potential mechanisms for tolerance of diazepam and

other benzodiazepines, including receptor de-sensitization, internalization, re-assembly with other subunits, and other compensatory changes modulating neurosteroids and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Clinically, tolerance for the anticonvulsant effect of diazepam can be seen in days and no efficacy data for usage longer than 4 months are available. Similar limited data are available for lorazepam and clonazepam.

### Other Indications for Use

Diazepam is a benzodiazepine and exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant, and amnesic effects. It is used in the management of anxiety disorders, alcohol withdrawal, and several disorders with skeletal muscle spasms. Clonazepam is indicated for the treatment of panic disorders with or without agoraphobia. Lorazepam is indicated as a preanesthetic medication to induce sedation, relieve anxiety, and reduce the ability to remember events related to the day of surgery.

### Adverse Effects

Adverse events occur in a dose-dependent manner with drowsiness, sedation, confusion, and amnesia been frequently reported. In some cases, these adverse events may decrease in severity with time.

### Toxicity, Overdose, and Contraindications

Benzodiazepines should not be used in patients with a history of sensitivity to this class of drugs or in patients with significant hepatic disease. They are also contraindicated in patients with acute angle glaucoma. Toxic overdose of benzodiazepines is associated with respiratory depression, coma, and even death. Benzodiazepines can worsen seizures, including an increase incidence of generalized tonic-clonic seizures. It is unclear as to whether this is a withdrawal symptom or unrelated to serum concentrations. There is also an increased risk of congenital malformations.

### Warning and Precautions

Benzodiazepines interfere with cognitive and motor performance, and patients should avoid the concomitant use of alcohol or other CNS-depressant drugs. Suicidal behaviors and ideation have been reported. Respiratory depression and coma are a concern.

### Special Safety Concerns

Benzodiazepines are Schedule IV controlled substances. Gradual discontinuation of these medication is needed, particularly in those patients who have been taking this class of drugs for more than a week.

### Teratogenicity Information

Diazepam, lorazepam, and clonazepam are pregnancy category D drugs.

### Drug Interaction

The CNS-depressant effects of all benzodiazepines are likely potentiated by alcohol, narcotics, and barbiturates, among other CNS-depressant medications. Cytochrome P-450 inducers induce the metabolism of clonazepam and diazepam by about 30% to 50%, lower than expected for plasma levels. Lorazepam is metabolized by glucuronidation, which can be inhibited by valproic acid in a similar manner as the interaction between valproic acid and lamotrigine. Oral contraceptives increase the hepatic metabolism of lorazepam.

### Use in Special Populations

Clearance of benzodiazepines, which tend to be lipophilic molecules, is lower in neonates and the elderly. Metabolism for these drugs also is slower in both special groups. If a benzodiazepine is needed by patients with hepatic or renal insufficiency, lorazepam is the preferred medication due to glucuronidation metabolism. The metabolite of lorazepam is removed by about 40% during a typical hemodialysis.

### Pediatric Use

Limited pharmacokinetic data exist in neonates, infants, and children.

## CARBAMAZEPINE

### Indications

Carbamazepine is recommended as a first-line therapy for patients with newly diagnosed partial seizures and for patients with primary generalized convulsive seizures who are not in an emergent situation.

### Dosing

The initial dose for carbamazepine in adults is 200 mg twice daily, increasing the daily dose to 600 to 1200 mg within a few weeks. There are several preparations including suspension and tablets of immediate or extended release. Doses may be started at one-fourth to one-third the anticipated maintenance dose and increased every 2 to 3 weeks. Because of the autoinduction of carbamazepine metabolism, within a few weeks from onset, it is necessary to administer the immediate-release formulation two to four times per day. The variable contributions of the 10,11-epoxide metabolite and free-carbamazepine concentrations have limited a more precise definition of the therapeutic range. Loading doses of

carbamazepine are indicated only for critically ill patients. The systemic clearance of carbamazepine also increases with time.

### Pharmacology

The mechanism of action of carbamazepine is believed to mainly enhance fast inactivation of voltage-gated sodium channels (ie, sodium channel antagonist). Other effects on ion channels that may contribute to its activity include interaction with voltage-gated calcium and potassium channels. The absorption of carbamazepine from immediate-release tablets (Tegretol) is slow and erratic due to its low water solubility. There is also large variability (up to 40%) in the peak-to-trough concentrations and there is no significant first-pass metabolism through the liver. Food, especially fat, may enhance the bioavailability of carbamazepine. Carbamazepine suspension is absorbed faster than the tablet form. Controlled-release (Tegretol-XR) and sustained-release (Carbatrol) preparations are also available, and are bioequivalent in twice daily (every 12 hours) dosing to immediate-release carbamazepine dosed four times daily (every 6 hours). Compared with immediate-release carbamazepine (Tegretol), both of the extended-release formulations have lower peaks and higher troughs serum levels, which may decrease peak side effects and improve seizure control, respectively. Sustained-release formulations improve overall tolerability and can improve Quality-of-Life (QOL) measurements as compared to the immediate-release formulation. Patients should be told to take Tegretol-XR with food and that the casing will be excreted in the feces, not indicating lack of absorption. Extended-release formulations cannot be broken or crushed. Tegretol-XR and Carbatrol appear to be bioequivalent; however, there is less variability in the absorption of Carbatrol. Carbamazepine is a neutral and highly lipophilic drug that is highly protein bound to  $\alpha$ 1-acid glycoprotein and albumin. Carbamazepine is metabolized primarily by CYP3A4 and its major metabolite is carbamazepine-10,11-epoxide, which has anticonvulsant activity in animals and humans. The formation of the 10,11-epoxide is influenced by concurrent use of other enzyme-inducing or enzyme-inhibiting drugs; thus, the 10,11-epoxide concentration may change with the administration of other drugs (eg, valproic acid and felbamate) with no change in parent carbamazepine concentration. Carbamazepine induces its own metabolism (autoinduction) within a few weeks, decreasing its half-life after chronic therapy. The presence of other CYP3A4-inducing drugs reduces the half-life of carbamazepine even more. The enzyme-induction effect begins within 3 to 5 days of starting therapy and takes 21 to 28 days to fully induce. Therefore, it is possible to achieve initial concentrations that are within the therapeutic range but have concentrations fall rather quickly despite continued therapy and good compliance. Some patients who respond well to initial therapy may be labeled refractory or noncompliant if the autoinduction phenomenon is not considered. The autoinduction reverses

rapidly if carbamazepine is discontinued. Carbamazepine also displays diurnal variation in its serum level with evening levels lower than morning levels. It appears that carbamazepine is cleared significantly faster in females than in males, and in Caucasians compared to African Americans, and therefore variable dosing may be needed. Polymorphisms of CYP3A4 have been described and might account for some of the ethnic and racial differences.

### Efficacy Data

Carbamazepine has been well studied in randomized controlled clinical trials. The VA Cooperative Study #118 compared the efficacy and toxicity of four antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, and primidone) for the treatment of partial and secondarily generalized tonic-clonic (GTC) seizures in over 600 adult male Veterans. The study was double-blinded and randomized, following patients for up to 36 months. Carbamazepine was shown to not only have superior tolerability and equal efficacy for secondarily GTC seizures but to also have superior efficacy for all partial seizures as compared to phenobarbital and primidone (1).

### Other Indications for Use

Carbamazepine is indicated for the treatment of painful trigeminal neuralgia. It might also be helpful in other painful neuropathies. There is some evidence supporting its use as a mood stabilizer, but does not have an FDA-approved indication.

### Adverse Effects

Carbamazepine side effects can parallel the rise and decline of serum concentrations daily. Neurosensory side effects are the most common (35% to 50% of patients). These side effects are more common during initiation of therapy and often resolve with continued treatment. Carbamazepine can also cause nausea, which can be caused by a local effect of the drug on the gastrointestinal (GI) tract, in which case food may help, or it can be caused by an effect on the brainstem, which may ultimately require discontinuation of the drug. Dosage manipulation, including the use of the controlled or sustained-release preparations, should be tried before the patient is considered to be intolerant of carbamazepine. Carbamazepine can cause hyponatremia, the incidence of which increases with age; however, its occurrence is lower than that seen with oxcarbazepine. Periodic determinations of serum sodium concentration are recommended, especially in the elderly. Leukopenia is the most common hematologic side effect, with an incidence as high as 10%. It usually is transient, even when the drug is continued, and can be caused by a redistribution of WBCs rather than a decrease in their production. In about 2% of patients, leukopenia is persistent, but even patients with WBC counts of  $3,000/\text{mm}^3$  ( $3 \times 10^9/\text{L}$ ) or

less do not seem to have an increased incidence of infection. A clinical guide is to continue carbamazepine therapy unless the WBC count drops to less than  $2,500/\text{mm}^3$  ( $2.5 \times 10^9/\text{L}$ ) and the absolute neutrophil count drops to less than  $1,000/\text{mm}^3$  ( $1 \times 10^9/\text{L}$ ). There are several case-control studies that have shown that patients of Chinese ancestry with the HLA-B\*1502 polymorphism might be at greater risk for developing Stevens-Johnson syndrome or other serious dermatologic reactions. Another polymorphism with a strong association with serious hypersensitivity reactions is the HLA-A\*3101 allele, which is found in people with European, Korean, and Japanese ancestry. Teratogenic effects have been observed.

### Toxicity, Overdose, and Contraindications

Toxicity after a large ingestion of carbamazepine is typically seen with 1 to 3 hours with a confusional state, ataxia, muscle twitching, rigidity, urinary retention, tachycardia, hypotension, and nausea and vomiting. The patient will require hospital monitoring for supportive treatment of respiratory failure and hypotensive shock. Induction of vomiting and use of activated charcoal might reduce some of the absorption of an overdose. Dialysis might be needed if renal failure occurs.

Carbamazepine is contraindicated in patients with prior bone marrow depression and hypersensitivity reactions to any tricyclic compounds, including antidepressants and carbamazepine. It should not be coadministered with nefazodone. It will reduce the plasma concentrations of many medications metabolized by CYP3A4, including birth control pills, many statins, and antiviral and chemotherapeutic drugs. As with many other anticonvulsants, suicidal behavior and ideation have been observed in a greater frequency in patients using carbamazepine.

### Warning and Precautions

Use of carbamazepine is associated with serious dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. There is evidence for an association of these dermatological reactions and the HLA-B\*1502 allele, particularly in Oriental populations, where the risk for these reactions is 10 times greater than in Western countries. There is also an association between these dermatological reactions and the HLA-A\*3101 allele seen in European, Japanese, Korean, Chinese, Southern Indian, Arabic, African American, and Native American ancestries. There is also evidence of aplastic anemia and agranulocytosis that is 5 to 8 times greater than in the general population (about 2–6 per one million exposures per year).

### Special Safety Concerns

Carbamazepine is a tricyclic structure that has some molecular resemblance to tricyclic antidepressants, which might have mild anticholinergic activity. Caution with increased

intraocular pressure and urinary retention is needed. Carbamazepine may also precipitate acute attacks in patients with hepatic porphyrias.

### Teratogenicity Information

Carbamazepine is a pregnancy category D drug. There is solid epidemiological data demonstrating an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Folic acid supplementation is important for all women of childbearing age potential taking carbamazepine.

### Drug Interaction

Carbamazepine increases the metabolism of many medications because of its potent effect inducing several of the CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4. Because of concentration-dependent efficacy and side effects, drug interactions with carbamazepine often are very significant. Drugs that inhibit CYP3A4 potentially may increase carbamazepine serum concentrations, while drugs that induce CYP3A4 may reduce carbamazepine serum concentrations.

### Use in Special Populations

Carbamazepine has been studied in children, elderly, and during pregnancy. It also has been used in patients with renal insufficiency. Given its potent hepatic induction properties and very rare association inducing hepatic failure, it is rarely used in patients with severe hepatic insufficiency.

### Pediatric Use

In children, between 6 and 12 years of age, the initial dose is 100 mg twice daily and increasing the dose to 400 to 800 mg after the autoinduction of its metabolism. Children over 12 years of age typically use adult dosing. Under 6 years of age, the dose is 10 to 20 mg/kg/day in twice or thrice daily schedule.

## ETHOSUXIMIDE

### Indications

Ethosuximide is indicated for the treatment of absence epilepsy.

### Dosing

Absence epilepsy is typically seen in children but might persist into adulthood. The initial dose in children ages 3 to 6 is 250 mg orally per day, and in children over age 6 is 500 mg orally per day. Every 4 to 7 days, the dose can be titrated upward by 250 mg until the patient achieves control of the seizures with



minimal or no side effects. Daily dosages exceeding 1,500 mg should be divided into 2 or 3 smaller doses during the day. Optimal pediatric dose is typically about 20 mg/kg/day, which results in a serum plasma level of 40 to 100 mcg/mL.

### Pharmacology

The mechanism of action of ethosuximide is believed to be inhibition of T-type calcium channels, which control the oscillatory behavior of some thalamic neurons. Ethosuximide is metabolized in the liver by hydroxylation, and the metabolites are believed to be inactive. There is some evidence of nonlinear pharmacokinetics at higher concentrations.

### Efficacy Data

Ethosuximide was shown to be superior to lamotrigine, and equal to valproic acid, in controlling absence seizures in a one-year double-blind, randomized controlled trial of 453 children with absence epilepsy. Ethosuximide had superior tolerability as compared to valproic acid. Maximal target doses were 60 mg/kg/day or 2,000 mg/day of ethosuximide.

### Other Indications for Use

There are no other indications for use.

### Adverse Effects

The most frequently reported side effects are nausea and vomiting (up to 40% of patients), which may be minimized by administration of smaller and more frequent doses. Rash is infrequent but has been noted. Other adverse events include sleep disturbances, dizziness, and attention problems.

### Toxicity, Overdose, and Contraindications

Patients with a history of hypersensitivity to succinimides should avoid taking ethosuximide. Toxic overdoses may produce not just acute gastrointestinal upset (ie, nausea, vomiting) but also CNS depression including coma with respiratory depression.

### Warning and Precautions

Use of ethosuximide has been associated with blood dyscrasias such as aplastic anemia. Abnormal liver and renal function have been reported in rare cases.

### Special Safety Concerns

Ethosuximide increases the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.

### Teratogenicity Information

Ethosuximide has not been awarded a Pregnancy category by the FDA. Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. Cases of birth defects have been reported with ethosuximide.

### Drug Interaction

Ethosuximide has few pharmacokinetic interactions. Ethosuximide is not protein bound, and, thus, displacement interactions do not occur. Valproic acid may inhibit the metabolism of ethosuximide, but only if its metabolism is near saturation. Ethosuximide may elevate phenytoin serum levels. The mechanism of this drug interaction is unclear.

### Use in Special Populations

Ethosuximide is primarily used in children and adolescents.

### Pediatric Use

A loading dose is not required. Titration over 1 to 2 weeks to maintenance doses of 20 mg/kg per day usually results in therapeutic concentrations. Data suggest that patients can be managed successfully on once-a-day therapy; however, GI distress appears to be dose related, and the total daily dose is usually divided into two equal doses.

## PHENOBARBITAL

### Indications

Phenobarbital is indicated for the management of tonic-clonic seizures and partial seizures in monotherapy or adjunctive therapy. It is also indicated for the prevention of febrile seizures in infants and young children, and for the prophylactic management of epilepsy. Phenobarbital also indicated as a second-line agent in status epilepticus.

### Dosing

Phenobarbital is available in oral and intravenous or intramuscular formulation. For seizure disorders, the typical doses are 15 to 50 mg twice or three times per day. In status epilepticus, the parenteral dose is 15 to 20 mg/kg/day.

### Pharmacology

The mechanism of action of phenobarbital is by interacting with GABA receptors to facilitate intrinsic chloride channel function, by blocking high voltage-activated calcium channels, and by blocking the glutaminergic AMPA and kainate receptors. The effect in GABA<sub>A</sub> receptors results in prolonged openings of the chloride channels, while the effect

on the glutaminergic receptors requires high concentrations. Phenobarbital is absorbed rapidly and completely regardless of whether it is given orally, intramuscularly, or rectally. It penetrates the brain at a rate comparable with that of phenytoin, and peak concentrations are achieved 3 to 20 minutes after an IV dose. Drugs affecting liver enzymes can alter phenobarbital metabolism, but phenobarbital clearance is not affected by liver blood flow. The elimination of phenobarbital is linear. Because tubular reabsorption of phenobarbital is pH dependent, the amount excreted renally can be increased by giving diuretics and urinary alkalinizers. Clearance decreases in the elderly. In nonacute situations, phenobarbital should be started in low doses and titrated upward. The dose–concentration relationship is linear. Because the half-life of phenobarbital is long, about 90 to 96 hours, doses can be given once daily, and bedtime dosing may minimize CNS depression. Phenobarbital has linear and predictable pharmacokinetics. Multiple dosage forms (eg, oral solid, oral liquid, IM, and IV) are available, and it is the most inexpensive AED. It is an enzyme inducer and interacts with many other drugs metabolized by the cytochrome P450 system. Phenobarbital has a very long half-life, and dosage adjustments should not be made more often than every 2 to 3 weeks. The parenteral product contains 67% to 75% propylene glycol and 10% alcohol, which can result in significant respiratory depression and hypotension if infused too rapidly.

### Efficacy Data

Phenobarbital was one of the agents examined in the first VA Cooperative study; it was shown to be comparable in efficacy to carbamazepine, phenytoin, and primidone, but had lower tolerability than carbamazepine and phenytoin.

### Other Indications for Use

Phenobarbital is indicated for the relief of anxiety and short-term treatment of insomnia. It can also be used perioperatively to relieve anxiety and induce sedation. Phenobarbital can be used during drug withdrawal from barbiturates or other nonbarbiturate hypnotics. Given its potent hepatic-inducing effect for CYP450 enzymes, it has been indicated for the prevention and treatment of hyperbilirubinemia in neonates and in cholestasis.

### Adverse Effects

CNS side effects are the primary factors limiting the use of phenobarbital. Tolerance usually develops to initial complaints of fatigue, drowsiness, sedation, and depression. Phenobarbital has significant side effects, including delayed intellectual development and hyperactivity in children and significant cognitive impairment in adults. It may also cause porphyria and rash, including serious rashes such as Stevens–Johnson syndrome. Rashes are seen in all ages, typically in less than 10% of subjects.

### Toxicity, Overdose, and Contraindications

Toxic effects and fatalities have been reported after overdoses with phenobarbital, a potent CNS depressant. Evaluation of respiratory function is needed. Phenobarbital is contraindicated in patients with known hypersensitivity to barbiturates, and in those with severe hepatic impairment or with history of porphyria. Patients with history of addiction to hypnotics and/or sedatives should avoid phenobarbital. If dyspnea or respiratory obstruction is evident, phenobarbital is also contraindicated.

### Warning and Precautions

The concomitant use of alcohol, sedatives, tranquilizers, or other CNS depressants with phenobarbital should be discouraged. Phenobarbital might reduce reaction time and impair the performance of potentially hazardous tasks such as driving or operating machinery. Phenobarbital is a potent inducer of CYP450 hepatic enzymes; thus, it potentially has a great number of drug interactions.

### Special Safety Concerns

Aplastic anemia, hepatic failure, and severe dermatologic rashes such as Stevens–Johnson syndrome have been reported in patients taking phenobarbital. The effectiveness of many drug therapies metabolized in the liver such as antibiotics, antiviral, anticoagulants, antichemotherapeutic agents, and statins might be significantly reduced. Phenobarbital is a controlled Schedule IV substance.

### Teratogenicity Information

Phenobarbital has been assigned to pregnancy category D and is a known teratogen.

### Drug Interaction

Phenobarbital is a potent enzyme inducer and can increase the elimination of any drug metabolized by CYP450- or glucuronidation (UGT)-mediated metabolism. Cimetidine and chloramphenicol inhibit phenobarbital metabolism, necessitating a decrease in dose. Ethanol increases the metabolism of phenobarbital.

### Use in Special Populations

Phenobarbital may be useful given IV in refractory status epilepticus.

### Pediatric Use

Phenobarbital is the drug of choice for neonatal seizures, but in other situations it is reserved for patients who have failed therapy with other AEDs.

## PHENYTOIN

### Indications

Phenytoin is indicated for the management of tonic-clonic seizures and psychomotor seizures in monotherapy or adjunctive therapy. It is also indicated for the prevention of seizures occurring during or following neurosurgery and the control of generalized tonic-clonic status epilepticus.

### Dosing

Phenytoin is available in several oral formulations, including the extended-release form known as phenytoin sodium (ie, Dilantin). There are several intravenous formulations such as phenytoin sodium and a prodrug, fosphenytoin. Fosphenytoin can be used with an intramuscular administration route. Phenytoin sodium can NOT be used in the intramuscular route since the pH of the salt formulation will create severe tissue injury. For seizure disorders, the typical doses are 15 to 50 mg, two or three times per day. Because of saturable absorption, an oral loading dose, such as 20 mg/kg, should be divided into four equal doses and given at 6-hour intervals. Subsequent dosage adjustments should be done cautiously owing to its nonlinear elimination. In status epilepticus, the parenteral loading dose is 15 to 20 mg/kg/day, at a rate not to exceed 1 to 3 mg/kg/min or 50 mg per minute, whichever is slower. Fosphenytoin is dosed in Phenytoin Equivalent (PE) units, which are the unit equivalent of the prodrug that will be converted into phenytoin in serum by phosphatases.

### Pharmacology

The mechanism of action of phenytoin is a voltage-dependent blockade of repetitive voltage-gated sodium channel activation. The bioavailability of the extended-release formulation is about 90%, and higher for other oral formulations. The bioavailability of phenytoin is almost complete for the intravenous and intramuscular formulations. Phenytoin is highly protein bound. It enters the brain rapidly and is redistributed to other body fluids and tissues, including breast milk and the placenta. Serum concentrations between 10 and 20 mcg/mL are typically associated with therapeutic effect and no clinical signs of toxicity. The half-life of phenytoin in the serum ranges from 10 to 15 hours after an intravenous administration. Its clearance tends to decrease with increasing patient age. Phenytoin is metabolized by the hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19 via a parahydroxylation reaction. The elimination of phenytoin is nonlinear, at least a two-rate kinetics. At low doses, most of the metabolism is due to CYP2C9, but when this isoenzyme is saturated with increasing serum concentrations, CYP2C19 is able to metabolize phenytoin at a slower pace, resulting in a steeper increase in the dose-level curve. The clinical importance of this is that a small change in dose can result in a disproportionately large increase in serum concentrations,

potentially leading to toxicity. Phenytoin penetrates the brain at a rate comparable to phenobarbital, and peak concentrations are achieved 3 to 20 minutes after an IV dose. Drugs affecting liver enzymes can alter phenytoin metabolism. It is an enzyme inducer and interacts with many other drugs metabolized by the cytochrome P450 system. Furthermore, there are several polymorphisms for the saturable CYP2C9 metabolism as well as for CYP2C19 metabolism with different degrees of function.

### Efficacy data

Phenytoin was one of the agents examined in the first VA Cooperative Study, where it was shown comparable in efficacy to carbamazepine, phenobarbital, and primidone, but had better tolerability than phenobarbital and primidone. Phenytoin was also used as adjunctive serial therapy in a randomized blinded study of convulsive status epilepticus of 518 Veterans.

### Other Indications for Use

There are no other approved indications for the use of phenytoin.

### Adverse Effects

CNS side effects are the primary factors limiting the use of phenytoin. Phenytoin has significant side effects such as nausea, fatigue, drowsiness, sedation, nystagmus, dizziness, and ataxia. Tolerance usually develops to the neurological adverse events after initial complaints. Some patients develop gingival hyperplasia and hypertrichosis and it can also exacerbate porphyrias. Phenytoin may also cause allergic rash, including serious rashes such as Stevens—Johnson syndrome. Rashes are seen in all ages, typically in less than 10% of subjects.

### Toxicity, Overdose, and Contraindications

It is estimated that the lethal dose of phenytoin in adults is about 2 to 5 grams.

Generalized toxicity typically involves nausea, vomiting, nystagmus, cardiovascular instability, and coma. Phenytoin is contraindicated in patients with a history of hypersensitivity to hydantoins and in patients with cardiac arrhythmias, such as sinus bradycardia, sino-atrial block, second- and third-degree A-V block, and Adams-Stokes syndrome. Coadministration of phenytoin with a class of nonnucleoside reverse transcriptase inhibitors such as delavirdine is contraindicated. Serious dermatological reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, particularly among people with HLA-B\*1502 polymorphism of the HLA-B gene. Multiorgan failure and drug reactions with eosinophilia have also been reported. There are rare cases of acute hepato-toxicity and

suppression of hematological cell lines have been observed. At very high concentrations of greater than 50 mcg/mL (200  $\mu$ mol/L), phenytoin can exacerbate seizures. Local toxicity to intravenous phenytoin sodium near the site of infusion might vary from minimal soft tissue irritation to extensive necrosis and limb ischemia, the so-called purple glove syndrome.

### Warning and Precautions

There are significant cardiovascular risks, including hypotension and cardiac arrhythmias, associated with rapid infusion of intravenous phenytoin sodium. Careful cardiac monitoring is required. Phenytoin is a potent inducer of CYP450 hepatic enzymes; thus, it has a great number of potential drug interactions.

### Special Safety Concerns

Aplastic anemia, hepatic failure, and severe dermatologic rashes such as Stevens–Johnson syndrome have been reported in patients taking phenytoin. The effectiveness of many drug therapies metabolized in the liver such as antibiotics, antiviral, anticoagulants, antichemotherapeutic agents, and statins may be significantly reduced.

### Teratogenicity Information

Phenytoin has been assigned to pregnancy category D and is a known teratogen.

### Drug Interaction

Phenytoin is associated with many interactions with other drugs involving altered absorption, metabolism, and protein binding that can enhance or reduce its effects. The absorption of phenytoin can be increased or decreased with the administration of food, depending on the composition of the meal. The bioavailability of phenytoin suspension can be decreased in patients receiving continuous enteral nutrient tube feedings. However, a single-dose study of simultaneous administration of enteral feeding found no difference in phenytoin bioavailability, suggesting that the mechanism was something other than physical contact. Phenytoin is a potent inducer of both hepatic CYP450 and glucuronidation (UGT) isoenzymes, and even induces its own CYP2C9 and CYP2C19 metabolism. Drug charts are available online and in the packet insert, but any medication that depends upon hepatic metabolism for its clearance, or if it induces or inhibits CYP2C9 should be considered as a potential target for a drug–phenytoin interaction.

### Use in Special Populations

Patients with hypoalbuminemia, renal, and/or hepatic insufficiency typically have an increased fraction of

unbound phenytoin. The active fraction of phenytoin is only about 10% of the total serum level, which is what is typically measured clinically. In these patient populations, carefulness in dosing is critical as the point of clinical toxicity might be achieved at lower total serum concentrations. The clearance of phenytoin is primarily based upon the metabolism of the hepatic isoenzyme, CY2C9. The serum concentration necessary to saturate CY2C9 activity appears to decrease in elderly patients. The intravenous formulation are likely useful in refractory status epilepticus.

### Pediatric Use

In pediatric populations, a typical loading dose would be 15 to 20 mg/kg of phenytoin or fosphenytoin PE.

## VALPROIC ACID

### Indications

Valproic acid (Depakene) and its derivatives, including valproate sodium (Depacon) and divalproex sodium (Depakote), are indicated for the treatment of simple and complex absence seizures and for the therapy of complex partial seizures. This is in monotherapy and/or in adjunctive therapy. Valproic acid is also indicated as adjunctive therapy for the treatment of multiple seizure types. Guidelines from several professional organizations (American Academy of Neurology, American Epilepsy Society, International League Against Epilepsy, National Institute for Health and Care Excellence) recommend these compounds as the first-line therapy for primary generalized seizures, including myoclonic, atonic, and absence seizures. These compounds will be discussed further under the term valproic acid, as it is the active compound at the site of the presumed mechanism of action. The compounds of the valproic acid family are available in several oral formulations for immediate release (tablets, sprinkles, syrup, enteric-coated) and in several extended-release presentations. In addition, intravenous formulation of valproate sodium can be used in the patients in whom the oral administration of valproic acid is indicated but temporarily not feasible.

### Dosing

For adults and children over age 10 years, therapy should be initiated at 10 to 15 mg/kg/day. There are immediate-release formulations that require dividing the initial daily dose into two to four times smaller doses to allow for a steady serum level and avoid adverse events. Alternatively, some of the extended-release formulations can be given once a day, optimally at bedtime. The daily dose can be increased by 5 to 10 mg/kg/week until the desired clinical response is achieved. Elderly patients are more susceptible to adverse events and might require smaller initial doses. The usually accepted therapeutic range for valproic acid is 50 to 100 mcg/mL. There are controlled studies that



show added efficacy at concentration twice as high, but at the expense of adverse effects, particularly neurocognitive symptoms. Valproic acid in some patients may have a half-life long enough for once-daily dosing with enteric-coated divalproex, but more frequent dosing is the norm. Based on half-life data, twice-daily dosing is feasible with any valproic acid dosage form; however, children and patients taking enzyme inducers can require dosing three to four times daily. The serum concentration–dose relationship is curvilinear (eg, the concentration–dose ratio decreases with increasing dose) probably because of increasing free concentrations and a resulting increase in clearance. Valproic acid is available as a soft gelatin capsule, an enteric-coated tablet, a syrup, a “sprinkle capsule,” an extended-release formulation designed for once-daily dosing, and an IV formulation for replacement of oral therapy or in situations where rapid loading is necessary. This parenteral formulation must not be given IM, because it can cause tissue necrosis. The sprinkle capsule, designed to be opened and mixed with food, has a slower rate of absorption, which results in fewer fluctuations in the peak-to-trough ratio. The syrup is absorbed more rapidly than any solid dosage form. The enteric-coated divalproex tablet is not sustained release. It must be metabolized in the gut to valproic acid. The enteric coating reduces GI distress. The enteric coating causes delayed absorption, although once the enteric coating dissolves, sodium divalproex has absorption, metabolism, and elimination rates similar to those of the gelatin capsule. If a patient is switched from Depakote to Depakote-ER, the dose should be increased by 14% to 20%. Depakote-ER may be given once daily.

### Pharmacology

The mechanism of action of valproic acid is not entirely understood, and there are several lines of investigation suggesting multiple mechanisms of action. There are alterations in the synthesis and degradation of GABA, but these do not fully explain the antiseizure activity. Valproic acid may potentiate postsynaptic GABA responses, may have a direct membrane-stabilizing effect, and may affect potassium channels. It appears to be absorbed completely from available oral dosage forms when administered on an empty stomach. However, the rate of absorption differs among preparations. Peak concentrations occur in 0.5 to 1 hour with the syrup, 1 to 3 hours with the capsule, and 2 to 6 hours with the enteric-coated tablet. The extended-release formulation (Depakote-ER) is FDA approved for patients with migraine headache and epilepsy. The bioavailability of this formulation is approximately 15% less than that of enteric-coated divalproex sodium (Depakote). Valproic acid is extensively bound to albumin, and this binding is saturable. Accordingly, the valproic acid free fraction will increase as the total serum concentration increases. Because of this saturable binding, measurement of unbound serum concentrations may be a better monitoring parameter than the total

valproic acid serum concentration, especially at higher concentrations or in patients with hypoalbuminemia. The primary route of valproic acid metabolism is  $\beta$ -oxidation, although up to 40% of a dose may be excreted as glucuronide. At least 10 metabolites of valproic acid have been identified. Some of these may have weak anticonvulsant activity, and at least one metabolite may be responsible for the hepatotoxicity reported. One of the lesser oxidative metabolites, 2-propyl-4-pentenoic acid (4-ene-VPA), causes hepatotoxicity in rats. The formation of this metabolite is increased when valproic acid is given with enzyme-inducing drugs. Valproic acid displays diurnal elimination with lower evening serum levels occurring than morning levels. It crosses into the placenta, and concentrations may be up to five times higher in cord serum blood than in the mother due to higher binding in the fetal compartment.

### Efficacy Data

Formulations of valproic acid have been used as the primary comparator drug in patients with primary generalized epilepsies when other medications such as lamotrigine, levetiracetam, topiramate, and zonisamide were added in adjunctive therapy. In complex partial seizures, divalproex sodium was compared in blinded controlled trials to carbamazepine and found to have equal efficacy.

### Other Indications for Use

Valproic acid formulations have been indicated for the treatment of mania and the prophylaxis of migraine headaches in adults.

### Adverse Effects

The most frequently reported side effects are gastrointestinal, or GI (up to 20%), including nausea, vomiting, anorexia, as well as weight gain. Pancreatitis is rare. GI complaints may be minimized, but not totally alleviated, with the enteric-coated formulation or by giving the drug with food. Alopecia and hair changes are temporary, and hair growth returns even with continued dosing. Weight gain can be significant for many patients and is associated with an increase in fasting insulin and leptin serum levels. The increase in serum insulin is believed to be caused by the inhibition of metabolism of insulin by the liver. This has led to the development of insulin resistance in obese male and female subjects. Valproic acid causes minimal cognitive impairment.

The most serious side effect reported with valproic acid is severe hepatotoxicity. Hyperammonemia is common (50%) but does not necessarily imply liver damage. Most liver failure deaths have occurred in patients who were younger than 2 years of age, had mental retardation, and received multiple AEDs. Hepatotoxicity occurred early in the course of therapy. Patients who complain of nausea,

vomiting, lethargy, anorexia, and edema in the first 6 to 12 months of therapy should have liver function evaluated.

Multiple AEDs can alter the metabolism of valproic acid, leading to increased formation of the potentially liver-toxic 4-ene-VPA. Valproic acid has been shown to alter carnitine metabolism, and it has been postulated that a deficiency of carnitine alters fatty acid oxidation that could lead to both liver toxicity and hyperammonemia. However, valproic acid hepatotoxicity has occurred in a patient taking supplemental carnitine, and a prospective study demonstrated no effect on well-being when carnitine was added. Although carnitine can ameliorate hyperammonemia in part, it is expensive, and there are only limited data to support routine supplemental use in patients taking valproic acid. Thrombocytopenia and alterations in platelet aggregation occur in patients receiving valproic acid, and these phenomena are related to serum concentration. These blood coagulopathies may occur more frequently in children than in adults.

### Toxicity, Overdose, and Contraindications

As in the case of other anticonvulsants, a history of known hypersensitivity to valproic acid or any of the closely related compounds is a contraindication for their use as medications in the future. In addition, known mitochondrial disorders, urea cycle disorders, and significant hepatic dysfunction are also contraindications for the use of compounds in the valproic acid family.

### Warning and Precautions

Suicidal ideation or similar behaviors should be monitored in patients taking these anticonvulsants. Thrombocytopenia is not an uncommon side effect of chronic therapy with these agents, but severe thrombocytopenia leading to severe bleeding is uncommon. Hepatotoxicity can be fatal, and the risk is greater in neonates, infants, and children. Pancreatitis, hyperammonemia, and multiorgan hypersensitivity reactions have been observed rarely.

### Special Safety Concerns

Other alternatives to the use of valproic acid compounds should be examined in all women of childbearing potential. If therapy with these compounds is necessary, folic acid supplementation should be given. The physician should aim at the lowest possible daily dosage that controls the epileptic seizures in these clinical scenarios.

### Teratogenicity Information

Valproic acid is a known teratogen with documented increases in spina bifida and decreased cognitive development

(decreased intelligence quotient (IQ)) for the child after in utero exposure. The FDA has assigned a pregnancy category D for the indications of epilepsy and for manic episodes associated with bipolar disorder but a pregnancy category X for prophylaxis of migraine headaches.

### Drug Interaction

Because it is highly protein bound, other highly protein-bound drugs (eg, free fatty acids and aspirin) can displace valproic acid. However, adding valproic acid to a patient taking phenytoin will transitorily result in an increased free-fraction of phenytoin as valproic acid has a tighter binding to serum proteins, displacing some of the bounded phenytoin. Many of the hepatic inducers of CYP450 will increase the clearance of valproic acid, resulting in lower serum concentrations than otherwise expected. Felbamate increases valproic acid serum concentrations. Valproic acid can inhibit specific CYP450 isozymes, epoxide hydrolase, and glucuronidation (UGT) isozymes. The latter is an important source of valproic acid–drug interaction by inhibiting the metabolism of lamotrigine, easily tripling the half-life of lamotrigine. The addition of valproic acid to phenobarbital results in a 30% to 50% decrease in phenobarbital clearance and significant toxicity if the dose of phenobarbital is not reduced. Data also suggest that combination oral contraceptives may increase the clearance of valproic acid and lower serum levels by 20% (2). In addition, carbapenems, especially meropenem, can lower valproic acid levels. As a hepatic CYP450 enzyme inhibitor, it is involved in multiple drug–drug interactions.

### Use in Special Populations

In the elderly, the initial and target doses of valproic acid are lower than in adults by at least 20% to 25%. Children under the age of 2 have a significantly higher incidence of severe hepatotoxicity and these compounds should be avoided, if possible.

### Pediatric Use

The safety and tolerability of valproic acid formulations in pediatric patients is comparable to that in adults. However, the incidence of severe hepatotoxicity is significantly higher in neonates and children as compared to adults.

Though the AEDs discussed in this chapter are considered “traditional,” they remain in use today. In some patients, they offer treatment options when newer AEDs have failed. The efficacy of these AEDs is considered comparable to the newer ones; however, the side effects are often different and more severe. Despite the waning popularity of these traditional AEDs, practitioners must still know their attributes as they are still commonly used.

TABLE 26.1 Summary of First-Generation AEDs

**Benzodiazepines: Clonazepam, Diazepam, Lorazepam**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for convulsive seizures, particularly seizure clusters. Clonazepam useful for seizures associated with Lennox-Gastaut syndrome and absence seizures; diazepam and lorazepam useful for status epilepticus, lorazepam not FDA approved for seizures or status epilepticus	Clonazepam 0.5–4.5 mg/d in 3 divided doses. Diazepam 2–6 mg/d in 2–4 divided doses. Lorazepam 2–3 mg/d given in divided doses.	Clonazepam 4.5–20 mg/d. Diazepam 4–40 mg/d in 2–4 divided doses. Lorazepam 1–10 mg/d in 2–3 divided doses.	Clonazepam – initial: 0.01–0.05 mg/kg/d in 2–3 divided doses, maintenance 0.1–0.2 mg/kg/d in 2–3 divided doses. Diazepam 3–10 mg/day in divided doses, titrate as indicated.	GABA <sub>A</sub> receptor agonist	Drowsiness, sedation, confusion, amnesia	D	Interfere with cognitive and motor performance; avoid concomitant use with other CNS depressant medications; respiratory distress and coma are possible with overdose; discontinue with taper	CNS depressant effects potentiated by other CNS depressants like alcohol, narcotics, barbiturates; CYP450 inducers increase metabolism of clonazepam and diazepam; lorazepam metabolism inhibited by valproic acid, oral contraceptives increase metabolism of lorazepam

**Carbamazepine**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Partial, generalized tonic-clonic and mixed seizure patterns	400 mg/d in divided doses	600–1,200 mg/d in 2–3 divided doses	<6 years: 10–20 mg/kg/d in 2–3 divided doses, up to 35 mg/kg/d in 2–3 divided doses; 6–12 years: 200 mg/day in 2 divided doses, up to 1,000 mg/day in 2–3 divided doses; >12 years: 400 mg/day in 2 divided doses, up to 1,000–1,200 mg/day in 2–3 divided doses.	Enhance fast inactivation of sodium channels	Neurosensory, nausea, vomiting, hyponatremia, leukopenia, severe rash	D	Serious dermatological reactions – Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia	Induces several CYP450 isoenzymes, so reduces levels of drugs metabolized by CYP1A2, 2B6, 2C9, 2C19, 3A4; drugs that inhibit CYP3A4 increase carbamazepine levels

(continued)

Table 26.1 Summary of First-Generation AEDs (*continued*)

<b>Ethosuximide</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Absence epilepsy	500 mg/d	1,500 mg/d in divided doses	Starting dose: 3–6 years – 250 mg/day; >6 years – 500 mg/d; typical maintenance dose 20mg/kg/d in divided doses	Inhibition of T-type calcium channels	Nausea, vomiting, sleep disturbance, dizziness, attention problems	Not awarded	Blood dyscrasias such as aplastic anemia; abnormal liver and renal function	Valproic acid may inhibit metabolism of ethosuximide; ethosuximide may elevate levels of phenytoin
<b>Phenobarbital</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Generalized tonic–clonic and partial seizures in monotherapy or adjunctive therapy	30–60 mg/d	60–200 mg/d	3–6 mg/kg/d	Modulates GABA <sub>A</sub> receptors; blocks high voltage activated calcium channels; blocks AMPA receptors	Fatigue, drowsiness, sedation, depression, delayed intellectual development, hyperactivity in children, cognitive impairment in adults, porphyria, serious rash	D	Concomitant use with other CNS depressants is discouraged, serious rash can occur, aplastic anemia and hepatic failure reported	Potent inducer of CYP450 or UGT mediated metabolism, cimetidine and chloramphenicol inhibit phenobarbital metabolism, ethanol increases phenobarbital metabolism
<b>Phenytoin</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Generalized tonic–clonic and complex partial seizures; prevention and treatment of seizures following neurosurgery	300 mg/day	300–400 mg/d	5 mg/kg/d, increase up to 300 mg/d	Voltage-dependent blockade of repetitive voltage-gated sodium channel activation	Nausea, fatigue, drowsiness, sedation, nystagmus, dizziness, ataxia, gingival hyperplasia, facial hair growth	D	Hypotension and arrhythmia when given IV, severe dermatologic reactions, many drug interactions	Inducer of CYP450 and UGT isoenzymes so any drug using this pathway will be affected

(continued)



Table 26.1 Summary of First-Generation AEDs (*continued*)**Valproic Acid**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Simple and complex absence seizures, complex partial seizures in monotherapy or adjunctive therapy	10–15 mg/kg/day in 2–4 divided doses	60 mg/kg/day in 2–4 divided doses	Start with 10–15 mg/kg/d in 2–4 divided doses; maximum dose of 60 mg/kg/d in 2–4 divided doses	Potentiates GABAergic activity, membrane stabilizing effect, may affect potassium channels	Nausea, vomiting, anorexia, weight gain, alopecia, cognitive impairment	D	Pancreatitis, thrombocytopenia, hepatotoxicity, hyperammonemia, multi-organ hypersensitivity reaction	Valproic acid is highly protein bound so will affect other protein bound medications, phenytoin level increased, inhibits CYP450 and UGT isozymes and can affect levels of other drugs metabolized by these pathways (such as lamotrigine, phenobarbital), oral contraceptives can increase clearance of valproic acid, hepatic inducers of CYP450 can reduce level of valproic acid

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# Second-Generation Antiepileptic Drugs

*Kathryn Idol Xixis, Roha Khalid, and Mohamad A. Mikati*

In 1993, a new era in antiepileptic drug (AED) treatment commenced. After a hiatus of almost two decades, a new AED, felbamate, was approved by the U.S. Food and Drug Administration (FDA). The next decade saw several new AEDs come to market. These provided physicians and patients with many new treatment options, several of which offered different and improved efficacy and side effect profiles. In this chapter, these so-called second-generation AEDs will be discussed. Included in this discussion will be felbamate, lamotrigine, gabapentin, topiramate, levetiracetam, oxcarbazepine, and tiagabine. Table 27.1 (located at the end of the chapter) summarizes their various attributes.

## FELBAMATE

### Indications

Felbamate is recommended only in patients who have an inadequate response to alternative treatments or whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure that this drug has is outweighed by the benefits of treatment (1). Once these criteria are met and a written acknowledgment of the risks is received from the patient, felbamate can be considered for either monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization in adults. It can be used as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children as well (2,3). Additionally, felbamate has been used in the management of Landau-Kleffner syndrome and in the management of refractory infantile spasm. Felbamate is not indicated as a first-line antiepileptic treatment due to an extremely high risk of developing aplastic anemia and liver failure (4).

### Dosing

In individuals older than 14 years when used in monotherapy, felbamate is initiated at 1200 mg/day in 3 to 4 divided

doses. The dose can be increased by 600 mg every 2 weeks to 2,400 mg/day or 3,600 mg/day if clinically indicated. When converting to monotherapy, felbamate is initiated at 1,200 mg/day and the dose of concomitant AEDs is reduced by one-third. At week 2, the felbamate dose is increased to 2,400 mg/day while reducing the dosage of other AEDs by an additional one-third of their original dosage. At week 3, felbamate is increased to the maximum dose of 3,600 mg/day and dose of other AEDs is decreased further. When used as adjunctive therapy, felbamate is initiated at 1,200 mg/day in three times daily (TID) or four times daily (QID) dosing. The concomitant AEDs are decreased in dose by 20%. Felbamate can be increased in 1,200 mg increments every week to reach a maximum dose of 3,600 mg. Other AEDs may have to be reduced further in dose to minimize side effects. Felbamate is available in tablet form at doses 400 mg and 600 mg. There is also an oral suspension form whose concentration is 600 mg/5 mL. There is no IV felbamate.

### Pharmacology

The mechanism of action of felbamate appears to involve inhibition of *N*-methyl-D-aspartate (NMDA) receptor responses and potentiation of  $\gamma$ -aminobutyric acid (GABA) receptor responses.

The drug is extremely well absorbed after oral administration. About 90% of it appears in the urine and about 40% to 50% of this virtually unchanged while the rest is in the form of unidentified metabolites. Felbamate has a half-life of 20 to 23 hours, which is unaltered after multiple doses. Binding of felbamate to human plasma protein is independent of felbamate concentrations between 176 and 310 micrograms/mL. About 22% to 25% of felbamate binds to albumin depending on its concentration.

### Efficacy Data

Felbamate (3,600 mg/day) and low-dose valproate (15 mg/kg/day) were compared as monotherapy for partial

seizures in a multicenter and a single-center, double-blind efficacy study conducted over a period of 112 days. The study was not designed to demonstrate comparative efficacy of the two drugs because valproate was not used at maximal effective dose. In any case, it showed statistically significant reduction in seizure frequency in the felbamate group.

To establish efficacy of felbamate as adjunctive therapy in partial seizures a double-blind, placebo-controlled crossover trial was conducted. Felbamate (3,600 mg/day) and placebo were then compared in a group of patients who had their standard antiepileptic drugs reduced while undergoing evaluations for surgery of intractable epilepsy. The primary efficacy variable was time to fourth seizure. The median times to fourth seizure were greater than 28 days in the felbamate group and 5 days in the placebo group, which was statistically significant ( $P = 0.002$ ).

### Other Indications for Use

Felbamate is not used in the treatment of psychiatric disorders likely due to the risk of aplastic anemia and hepatotoxicity associated with its use (5).

### Adverse Effects

Adverse events occurred at an incidence of 2% or more among 58 adult patients who received felbamate monotherapy at dosages of 3,600 mg/day in double-blind controlled trials. Major side effects were fatigue, insomnia, and anxiety. Minor side effects seen were dyspepsia, vomiting, diarrhea, and constipation.

In add-on controlled trials at dosages up to 3,600 mg/day adverse events also occurred at an incidence of 2% or more among 114 adult patients who received felbamate as an adjunctive therapy. Many of these adverse experiences typically resolved with conversion to monotherapy, or with adjustment of the dosages of other antiepileptic drugs. The most common side effects were headache, somnolence, insomnia, and nervousness. In children, the major side effects were fever, fatigue, somnolence and insomnia, anorexia, and hyperactivity.

The risk of developing aplastic anemia or liver failure is the major factor in restricting the use of felbamate.

### Toxicity, Overdose, and Contraindications

Hepatic and aplastic anemia are idiosyncratic side effects. No serious adverse reactions have been reported specifically to overdosing. General supportive measures should be employed if overdosage occurs. It is not known if felbamate is dialyzable. It is contraindicated in patients in whom the risks of using it are not outweighed by the potential benefits (see the following sections, Warning and Precautions; and Special Safety Concerns).

### Warning and Precautions

The use of felbamate is associated with an increased incidence of aplastic anemia. Clinical manifestations of aplastic anemia may not be seen for several months after the initiation of use of felbamate. Once the drug is discontinued, the patient remains at a risk for developing aplastic anemia for an unknown amount of time. Patients on felbamate may be at more than a 100-fold greater risk for developing the syndrome than the general population.

There are not enough felbamate-associated cases of aplastic anemia to provide a reliable estimate of incidence or case fatality rate or to assess if there are any factors that place patients at greater or lesser risk. Felbamate has shown a risk of liver failure in about 6 cases per 75,000 patient-years of use. It is uncertain whether the risk of liver failure changes with duration of exposure or the dosage used. Therefore, felbamate should not be used in anyone with hepatic dysfunction. Moreover, felbamate should be discontinued if the liver enzymes are elevated greater than twice the upper limit of normal or if patient develops clinical signs and symptoms of liver failure.

### Special Safety Concerns

Aplastic anemia is a potential adverse effect of felbamate. At present there is no way to predict who is likely to get aplastic anemia, nor is there a documented effective means to monitor the patient so as to avoid and/or reduce the risk. Patients with a history of any blood dyscrasia should not receive felbamate. Any signs of infection, bleeding and easy bruising should be reported to the physician.

Another major safety concern is hepatic failure. There is no way to predict who is likely to develop hepatic failure. Patients with a history of hepatic dysfunction should not be started on felbamate. Any patient who is starting on felbamate should undergo liver function testing before using felbamate and at frequent intervals while taking it.

Like most other AEDs, felbamate also increases the risk of suicidal ideation in patients. Therefore, all patients should be monitored for emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

### Teratogenicity Information

Felbamate is a Pregnancy Category C drug. Animal studies did not show increased incidence of malformations compared to controls in offspring of rats or rabbits when given doses up to 13.9 times (rat) and 4.2 times (rabbit) the human daily dose on an mg/kg basis. However, in rats, there was a decrease in pup weight and an increase in pup deaths during lactation. The cause for these deaths is not known. The no-effect dose for rat pup mortality was 6.9 times the human dose on an mg/kg basis. Placental transfer of felbamate occurs in rat pups. There are, however, no studies in pregnant women.



### Drug Interaction (With AEDs and Other Commonly Used Medications)

Felbamate *increases* the steady-state plasma concentration of phenytoin, valproate, and phenobarbital, while *decreasing* the steady-state plasma concentration of carbamazepine. Effects of other drugs on felbamate: phenytoin and carbamazepine cause an increase in the clearance of felbamate, thus leading to a 40% to 45% decrease in the steady-state trough concentration. Valproate does not affect felbamate plasma levels, whereas phenobarbital can decrease felbamate levels by 29%. Antacids, erythromycin, and oral contraceptives do not alter its concentration.

### Use in Special Populations

The effect of felbamate on labor and delivery in human subjects is unknown. Although felbamate has been detected in human milk its effect on the nursing infant is unknown. No systematic studies in geriatric patients have been conducted. Clinical studies of felbamate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experiences have not identified differences in responses between the elderly and younger patients. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### Pediatric Use

The safety and effectiveness of felbamate in children other than those with Lennox-Gastaut syndrome has not been established. A 70-day double-blind, placebo-controlled trial was done to assess efficacy of felbamate as adjunctive therapy in children with Lennox-Gastaut syndrome. It was concluded that felbamate (45 mg/kg/day) was superior to placebo in controlling the multiple seizure types associated with this condition. Felbamate is started at 15 mg/kg/day in three or four times daily dosing while reducing background AEDs by 20%. Further reductions of the concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Felbamate can be increased by 15 mg/kg/day increments at weekly intervals to a maximum of 45 mg/kg/day.

## LAMOTRIGINE

### Indications

Lamotrigine is approved as an adjunctive therapy for patients aged two years or older in the treatment of partial seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome. For patients 16 years or older, lamotrigine is also approved as a

monotherapy alternative in patients who are being treated with carbamazepine, phenytoin, phenobarbital, primidone, or valproate. However, the safety and efficacy of lamotrigine as an initial monotherapy has not been established. Likewise, lamotrigine has not been studied as a monotherapy for patients previously maintained on antiepileptics other than the ones previously listed, and lamotrigine has not been studied as a monotherapy for a patient previously requiring two or more simultaneous antiepileptics (6).

### Dosing

Lamotrigine should be initiated slowly to reduce the risk of adverse effects. To determine appropriate dosing of lamotrigine in epilepsy patients, consideration must be made as to the patients' background antiepileptic regimens and whether or not they contain medications that are inducers or inhibitors of hepatic enzymes. For patients who are not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, lamotrigine therapy is initiated at 25 mg orally daily for weeks 1 and 2. This is increased to 50 mg orally daily for weeks 3 and 4. Subsequently, the lamotrigine dose can be safely increased by 50 mg per day every 1 to 2 weeks to a goal maintenance dose of 225 to 375 mg per day, divided into two equal doses. For patients who are taking valproate at the time of lamotrigine initiation, lamotrigine must be titrated more slowly as valproate acts as an inhibitor effectively increasing the dose of lamotrigine. For these patients, initial lamotrigine dose should be started at 25 mg orally every other day for weeks 1 and 2. This can be increased to 25 mg orally every day during weeks 3 and 4. Beginning in week 5, the total lamotrigine dose may be increased by 25 mg to 50 mg per day every 1 to 2 weeks to a goal dose of 100 mg/day to 200 mg/day, in one dose or two divided doses for a patient who will be continuing valproate concurrently with lamotrigine. For patients who will be continuing valproate, an inhibitor, as well as other medications that are inducers, after initiation of lamotrigine, goal maintenance dosing ranges between 100 mg/day and 400 mg/day, in one or two divided doses. Finally, for patients who are continuing carbamazepine, phenytoin, phenobarbital, or primidone, which are all inducing medications that decrease the effective dose of lamotrigine, a different titration is preferable. For these patients, initiation of lamotrigine should be at 50 mg/day for weeks 1 and 2 followed by an increase to 100 mg/day in two divided doses during weeks 3 and 4. From week 5 onward, lamotrigine can be safely increased by 100 mg/day every 1 to 2 weeks to a goal dose of 300 mg/day to 500 mg/day in two divided doses. Caution must be exercised when patients using lamotrigine start or stop estrogen-containing oral contraceptives as these medications have been shown to decrease lamotrigine levels in serum. Lamotrigine should not be abruptly discontinued but instead should be weaned off over an absolute minimum of 2 weeks with approximately 50% reduction per week.

## Pharmacology

The mechanism of action of lamotrigine appears to involve blocking voltage-dependent sodium channels, thus decreasing the release of excitatory neurotransmitters.

Lamotrigine has excellent oral bioavailability that is not affected by the presence of food. In studies, lamotrigine's peak plasma concentration was reached between 1.4 hours and 4.8 hours. Lamotrigine serum levels increase in direct proportion to increases in dosage. The volume of distribution of lamotrigine ranges from 0.9 L/kg to 1.3 L/kg. Lamotrigine is not significantly protein bound. In healthy volunteers, the half-life of single-dose lamotrigine was 32.8 hours and of multiple-dose lamotrigine was 25.4 hours. However, half-life of lamotrigine varies based on other medications that are used concomitantly. Lamotrigine is hepatically metabolized with minimal first-pass effect. This is of clinical significance as the levels of lamotrigine can be decreased or increased by concomitantly administered medications that induce or inhibit hepatic enzymes. A definitive therapeutic plasma concentration range for lamotrigine has not been established. Instead, dosing is best based on therapeutic response.

## Efficacy Data

Lamotrigine was established as an adjunctive therapy in adults with partial seizures, as an adjunctive therapy in pediatric patients with partial seizures, as an adjunctive therapy in adult and pediatric patients with primary generalized tonic-clonic seizures, and as an adjunctive therapy in adult and pediatric patients with Lennox-Gastaut Syndrome in a series of studies in which patients were maintained on their current antiepileptic regimens in addition to either lamotrigine or placebo. For patients taking valproate at baseline, lamotrigine target dosing was appropriately lowered. Two of the studies evaluating lamotrigine as adjunctive therapy in adults with partial seizures did not enroll any patients on valproate for ease of lamotrigine dosing. In studies evaluating lamotrigine as adjunctive therapy in adults with partial seizures, in children with partial seizures, and in adults and children with primary generalized tonic-clonic seizures, the seizure frequency of the respective seizure types showed a statistically significant reduction in favor of lamotrigine over placebo. Statistically significant reduction in major motor seizures, drop attacks, and tonic-clonic seizures were seen in the study investigating lamotrigine versus placebo in patients with Lennox-Gastaut syndrome.

## Efficacy in Other Conditions

Lamotrigine is approved for bipolar I disorder in adults who are 18 years or older as a maintenance treatment to prolong the time to occurrence of mood episodes (7). However, lamotrigine is not approved as therapy for the treatment of acute mood episodes as its effectiveness for this indication has not

been established. Some studies have also found lamotrigine useful in neuropathic pain syndromes, including trigeminal neuralgia, painful diabetic neuropathy, HIV-associated neuropathy, poststroke pain, postoperative pain, and cold-induced pain; however, additional trials are needed to establish the efficacy of lamotrigine in these conditions (8,9). Small studies have suggested benefit from lamotrigine in unipolar depression, schizophrenia spectrum disorders, borderline personality disorder, and depersonalization disorder as well.

## Adverse Effects

Adverse reactions noted in greater than 10% of adult patients in clinical studies include headache, dizziness, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Pediatric patients were additionally noted to have vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, and tremor in more than 10% of the patients in clinical studies.

## Toxicity, Overdose, and Contraindications

At extremely high doses and in overdose of lamotrigine, ataxia and nystagmus may occur. In fact, oculogyric crises have been reported in the setting of lamotrigine toxicity (10). In addition, decreased level of consciousness with progression to coma and with accompanying respiratory depression and death, intraventricular conduction delay, and increased seizure activity can be seen. Treatment for overdose is supportive as no specific antidote exists. Given that lamotrigine is metabolized through the liver, dialysis is unhelpful. A systemic allergic-type reaction similar to anticonvulsant hypersensitivity syndrome may also be seen in overdose (11).

## Warnings and Precautions

The most well known and one of the most dangerous potential adverse effects associated with lamotrigine is skin rash, which is rare, but for which lamotrigine holds a black box warning; specifically cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with its use. There is some evidence that patients who are also taking valproate are at higher risk of developing serious adverse skin effects. Multisystem hypersensitivity reactions or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been observed in patients taking lamotrigine, and lamotrigine has a black box warning for these. This typically presents with fever, rash, and lymphadenopathy in association with multiorgan involvement. Isolated liver failure has also occurred. A wide variety of blood dyscrasias and aseptic meningitis have also been seen in patients taking lamotrigine.

Antiepileptic drugs are known for increasing suicidal behavior and ideation, and patients must be monitored closely. This is especially important during initiation of the

medication and dosage changes. Lamotrigine should not be abruptly discontinued as increased seizure frequency has been noted.

Patients taking lamotrigine are at risk for sudden unexpected death in epilepsy (SUDEP) as well; however, studies do not demonstrate that the risk is higher with lamotrigine than with other antiepileptic medications. Lastly, lamotrigine is known to bind with melanin. As such, there is a possibility that lamotrigine could bind melanin-rich tissues and accumulate in those tissues over time. Studies have not proved or disproved the risk of injury after long-term exposure. At this time, there are no recommendations for monitoring this potential side effect, including no specific recommendations for ophthalmologic monitoring.

### Teratogenicity

Lamotrigine is Pregnancy Category C drug. No adequate studies regarding the use of lamotrigine in pregnant women exist, but ill effects have been observed in mice and rats. Of note is lamotrigine's inhibition of dihydrofolate reductase in animal studies that led to a decrease in overall folate levels. Results from the AED pregnancy registry study suggest a lower risk of malformations with lamotrigine than traditional AEDs. In the AED pregnancy registry study, 2% of neonates born to mothers taking lamotrigine were found to have a major congenital malformation. The most common malformation was oral clefting followed by cardiovascular abnormalities and neural tube defects. Furthermore, no apparent dose effect on likelihood of congenital malformation was appreciated (12).

### Special Safety Concerns and Monitoring

Special attention should be paid when lamotrigine is used in an antiepileptic regimen concomitantly with valproate, carbamazepine, phenytoin, primidone, phenobarbital, rifampin, and estrogen-containing oral contraceptive pills. This is discussed in more detail in the following. Monitoring of lamotrigine serum levels may be useful in determining levels associated with appropriate clinical response on a patient-by-patient basis, but no standard therapeutic range for lamotrigine has been established. While there are no current monitoring recommendations, blood counts and hepatic function should be checked on an as-needed basis to monitor for blood dyscrasias and hepatotoxicity, respectively (13).

### Drug Interactions

Significant drug interactions with lamotrigine involve the risk for increased or decreased active lamotrigine levels in the serum as a result of increased or decreased metabolism of lamotrigine. Concomitant use of lamotrigine and estrogen-containing oral contraceptive pills with ethinylestradiol and levonorgestrel have resulted in an approximate decrease in lamotrigine levels by 50% as well as a decrease in

levonorgestrel levels. Additionally, concomitant use of lamotrigine with phenobarbital, primidone, phenytoin, rifampin, carbamazepine decreases lamotrigine serum levels by as much as 40%. It is unclear if the interaction between lamotrigine and carbamazepine also increases the levels of carbamazepine epoxide, the active metabolite of carbamazepine. Lamotrigine and valproate taken together has been shown to almost double lamotrigine levels. The data regarding the effect of this interaction on valproate levels are unclear.

### Use in Special Populations

Decreased levels of lamotrigine have been reported during pregnancy with return to prepregnancy levels after delivery. As such, dose adjustment may be necessary in patients who continue on lamotrigine in pregnancy. Lamotrigine is present in human breast milk. Small studies have identified breastfed infants with lamotrigine levels approximately one-half of the level found in the mother. Further consideration must be made for infants of mothers whose lamotrigine dosages required increases during pregnancy as these infants may experience extremely high lamotrigine levels. As the hepatic metabolism of infants is immature, clearance of lamotrigine from the infant may be further delayed. Reported events in breastfed infants of mothers taking lamotrigine include drowsiness, poor sucking, and apnea. These events have not been directly correlated with lamotrigine use but care should be exercised (14).

Use of lamotrigine in patients over the age of 65 has not been sufficiently studied to determine whether or not these patients require a different safety profile from younger patients.

Studies of lamotrigine in patients with hepatic impairment are small and limited. It is generally felt that no dosage adjustment is necessary for mild hepatic impairment. In patients with moderate or severe hepatic impairment, dosing should be reduced by approximately 25%. If patients with severe hepatic impairment exhibit significant ascites, reduction of lamotrigine dosing by approximately 50% should be considered. Specific recommendations for lamotrigine dosage adjustment in renal insufficiency are unavailable.

### Pediatric Use

Lamotrigine is approved in children aged two years and older as an adjunctive therapy for partial seizures, primary generalized tonic-clonic seizures, and the generalized seizures of Lennox-Gastaut syndrome. The efficacy of lamotrigine in the treatment of Landau-Kleffner and infantile spasms has also been reported (2,15). Furthermore, lamotrigine has a long history of successful use in absence seizure and other primary generalized epilepsy syndromes in childhood (16). Some trials of lamotrigine in children under 24 months have shown that lamotrigine is associated with increased risk for infectious and respiratory adverse reactions. However, other studies have shown that lamotrigine



is effective and well tolerated in this age group (17,18). Similar to adults, dosing of lamotrigine in pediatrics depends on whether or not the patient is also taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate. For a patient not taking any of these medications at the time of the initiation of lamotrigine therapy, 0.3 mg/kg/day of lamotrigine in one or two divided doses should be administered during weeks 1 and 2. This can be increased to 0.6 mg/kg/day in two divided doses during weeks 3 and 4. From week 5 onward, the lamotrigine dose can be increased every 1 to 2 weeks by an additional 0.6 mg/kg/day. Maintenance dosing is 4.5 to 7.5 mg/kg/day with a maximum of 300 mg/day in two divided doses. For patients who are taking carbamazepine, phenytoin, phenobarbital, or primidone but not valproate, lamotrigine should be initiated at 0.6 mg/kg/day in two divided doses for weeks 1 and 2. This should be increased to 1.2 mg/kg/day in two divided doses during weeks 3 and 4. From week 5 onward, the lamotrigine dose can be increased every 1 to 2 weeks by an additional 1.2 mg/kg/day. Typical maintenance dosing is 5 to 15 mg/kg/day, with a maximum of 400 mg/day in two divided doses. For patients who are taking valproate but not carbamazepine, phenytoin, phenobarbital, or primidone, lamotrigine should be initiated at 0.15 mg/kg/day in one or two divided doses for weeks 1 and 2. This can be increased to 0.3 mg/kg/day in weeks 3 and 4 in one or two divided doses. From week 5 onward, the lamotrigine dose can be increased every 1 to 2 weeks by an additional 0.3 mg/kg/day. At such small doses, it is important to note that doses should be rounded down to the nearest whole tablet size. Typical maintenance dosing is 1 to 5 mg/kg/day with a maximum of 200 mg/day in one or two divided doses. If the only additional antiepileptic drug the patient is taking is valproate, a slightly lower target maintenance dose of 1 to 3 mg/kg/day is more appropriate. For children weighing less than 40 kg who are taking valproate but not carbamazepine, phenytoin, phenobarbital, or primidone, lamotrigine dosing can be difficult. The smallest available lamotrigine tablet is 2 mg, and this may be drastically too high for a small patient.

While the guidelines in the previous paragraph are safe, the following recommendations may be more easily applied in small patients. For initiation of therapy in weeks 1 through 4 in a 6.7 kg to 14 kg patient, start with 2 mg every other day in weeks 1 and 2 before transitioning to 2 mg daily in weeks 3 and 4. In a 14.1 kg to 27 kg patient, use 2 mg daily in weeks 1 and 2 before increasing to 4 mg daily in weeks 3 and 4. In a 27.1 kg to 34 kg patient, use 4 mg daily in weeks 1 and 2 before increasing to 8 mg daily in weeks 3 and 4. Lastly, in a 34.1 kg to 40 kg patient, use 5 mg daily for weeks 1 and 2 before increasing to 10 mg daily in weeks 3 and 4. The dosage can then be increased into week 5 and beyond as described earlier until maintenance dosing is reached. As referenced previously, with weight-based dosing in pediatrics tablets may not be available in the exact calculated dosages. Dosages should be rounded down to the nearest available

whole tablet size. Tablets should not be split. Additionally, maintenance dosing in patients less than 30 kg may need to be increased by as much as 50% in patients taking carbamazepine, phenytoin, phenobarbital, primidone, valproate, or lamotrigine alone and should be titrated according to clinical response.

## GABAPENTIN

### Indications

Gabapentin is indicated as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients aged 3 and older (19).

### Dosing

Gabapentin is an oral medication. The target dose of gabapentin for use in epilepsy patients aged 12 or older is 900 to 1,800 mg/day administered in three divided doses. Some studies have shown that many patients require and tolerate doses up to 2,400 mg/day. Doses up to 3,600 mg/day have been given. Patients are typically titrated to an initial goal dose of 900 mg/day in three divided doses over the course of a few days.

### Pharmacology

The definitive mechanism of action of gabapentin as an anticonvulsant and as an analgesic is unknown. Gabapentin is structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA), but gabapentin is not converted to nor does it interact with the functions of the neurotransmitter GABA. Some studies suggest that at least part of gabapentin's action may be related to its interaction with voltage-gated calcium channels.

Gabapentin is not metabolized in humans. Observed pharmacological actions are related to the parent compound. Of note, the oral bioavailability of gabapentin decreases as the dose is increased. The bioavailability of gabapentin is not significantly affected by interactions with food. Gabapentin is minimally bound to plasma proteins in distribution. The elimination of gabapentin is via renal excretion, and patients with renal insufficiency will require dose adjustment. The half-life of gabapentin is 5 to 7 hours. The half-life is not affected by differing doses or multiple doses.

### Efficacy Data

The efficacy of gabapentin as an adjunctive therapy in patients aged 3 and older with refractory partial seizures was evaluated in clinical trials in which gabapentin was tested versus placebo. Assessment of efficacy was through evaluation of the percentage of patients who experienced at least a 50% reduction in seizure frequency from baseline,



denoted as the responder rate, and through calculation of response ratios. The responder rates and the response ratios from these studies had mixed results with statistical significance achieved for one or both in some studies but not in others. Further analyses showed a statistically significant advantage of gabapentin over placebo in prevention of secondarily generalized tonic-clonic seizures when both responder rates and response ratios were analyzed. Gabapentin was also compared to placebo in studies that enrolled patients aged 1 month to 3 years, but no statistically significant difference was found in the response ratio or the responder rate in this group.

### Efficacy in Other Conditions

In addition to use as an adjunctive therapy for seizures, gabapentin is labeled for use in treatment of postherpetic neuralgia and restless leg syndrome (20). Gabapentin is widely used in and has been shown to be efficacious in a variety of conditions involving neuropathic pain, in addition to postherpetic neuralgia commonly including diabetic neuropathy and trigeminal neuralgia (21). A few studies have found gabapentin useful in the treatment of pain related to fibromyalgia, in the treatment of pain and spasticity associated with multiple sclerosis, and in the treatment of migraines as a prophylactic medication (22,23). A variety of other uses for gabapentin in addition to pain have been evaluated in small studies. These include gabapentin as a treatment for hot flashes, as a treatment for itching related to uremic pruritis, as a treatment for essential tremor, and as a treatment for some forms of acquired and congenital nystagmus (24–26). Gabapentin was investigated as a treatment against the progression of amyotrophic lateral sclerosis, but studies have not shown significant benefit (27). Gabapentin has been used in a variety of psychiatric illnesses, especially in anxiety disorders with mixed results. Gabapentin has also been investigated as a treatment for cocaine cravings.

### Adverse Effects

The most commonly noted adverse events in studies of patients older than 12 years taking gabapentin in combination with other antiepileptics, that were not reported at a similar frequency in patients receiving placebo in combination with other antiepileptics, include dizziness, ataxia, nystagmus, fatigue, and somnolence. Likewise, the most commonly noted adverse events in studies of patients aged 3 to 12 years of age taking gabapentin in combination with other antiepileptics, which were not reported at a similar frequency in patients receiving placebo in combination with other antiepileptics, include fever, viral infection, nausea, vomiting, somnolence, and hostility (28). Adverse effects observed in clinical trials were typically mild to moderate in intensity. Adverse effects including sweating, nausea,

anxiety, insomnia, and pain have also been reported with abrupt discontinuation of gabapentin.

### Toxicity, Overdose, and Contraindications

Animal studies testing doses up to 8000 mg/kg in a single administration have not identified a lethal dose of gabapentin. Signs of acute toxicity as demonstrated by animal studies include ataxia, ptosis, labored breathing, decreased activity, sedation, or excitation. Additional signs of acute toxicity have been reported in human overdoses of up to 49 grams including diplopia, slurred speech, diarrhea, drowsiness, and lethargy. Treatment is largely supportive. Gabapentin can be also removed by hemodialysis in cases where this is deemed necessary.

### Warnings and Precautions

Gabapentin, as with all antiepileptic drugs, carries a black box warning for suicidality. However, little specific data regarding gabapentin and suicidal thoughts or behavior are available. Neuropsychiatric adverse events have been noted in some patients between the ages of 3 and 12 taking gabapentin. These include, in order of highest to lowest incidence, emotional lability, hostility, hyperkinesia, and difficulty with concentration and changes in school performance. While recorded events have typically been mild to moderate in severity, one incidence of serious hostility was reported in clinical trials.

Abrupt withdrawal of gabapentin, as with other antiepileptic drugs, can lead to an acute increase in seizure frequency. Gabapentin should be tapered off over a minimum of 1 week. There are insufficient data to conclude whether or not patients treated with gabapentin experience an increased rate of status epilepticus compared to patients not treated with gabapentin.

Preclinical carcinogenicity studies on rats receiving gabapentin showed an increased incidence of pancreatic acinar adenocarcinomas in male rats. This was not found in female rats in the same study. The clinical significance of this is unknown. Clinical studies of epilepsy patients on gabapentin adjunctive therapy followed patients with new tumors and worsening preexisting tumors, but information is scant regarding whether or not populations treated with gabapentin experienced an increased incidence of tumors compared to populations not treated with gabapentin.

Studies assessing gabapentin and sudden unexpected death in epilepsy (SUDEP) noted that patients taking gabapentin for epilepsy did experience a higher incidence of sudden and unexplained deaths than an age- and sex-matched healthy population; however, this increased incidence fell within the range of incidence for epilepsy patients experiencing sudden and unexplained death who were not taking gabapentin. As with other antiepileptic medications,

DRESS has been reported in patients taking gabapentin. Some of these events have been life threatening or fatal.

### Teratogenicity

Gabapentin is classified as a category C medication. In animal studies, gabapentin has been shown to cause delayed bone ossification as well as increased incidence of hydroureter and hydronephrosis. The incidence of other malformations was not increased in animal studies. Of note, some animal studies have demonstrated an increased incidence of fetal loss in animals receiving gabapentin. Adequate studies have not been done on the use of gabapentin in human pregnancies. Gabapentin should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus. Additionally, orally administered gabapentin is secreted into human breast milk. The effect of gabapentin on infants is unknown.

### Special Safety Concerns and Monitoring

Laboratory monitoring of gabapentin levels or other parameters is not necessary. Gabapentin may be used in combination with other antiepileptic medications without concern for alteration in plasma levels of either gabapentin or the other antiepileptic medications. If discontinued, gabapentin should be tapered over the course of at least 1 week.

### Drug Interactions

Unlike many antiepileptic medications, gabapentin is not significantly metabolized by nor does it interfere with the metabolism of other commonly used antiepileptic drugs including phenytoin, carbamazepine, valproic acid, or phenobarbital. In addition, gabapentin does not significantly inhibit the major cytochrome P450 enzymes. Increases and decreases in gabapentin have been noted with coadministration of gabapentin and certain pain medications. For instance, in studies, coadministration of naproxen and gabapentin led to mild increase in gabapentin absorption. Coadministration of hydrocodone and naproxen led to reduction in hydrocodone levels and to increase in gabapentin levels. Coadministration of morphine and gabapentin led to increase in gabapentin levels. Concomitant use of gabapentin and oral contraceptives were not found to have clinically significant interactions. The bioavailability of gabapentin was decreased when administered with antacids, although this interaction was essentially nonexistent if gabapentin was taken at least 2 hours after the antacid medication.

### Use in Special Populations

Studies of gabapentin in epilepsy did not include sufficient numbers of elderly patients to determine whether elderly

patients respond differently than younger patients. Notably, however, in studies of gabapentin in postherpetic neuralgia, a larger treatment effect was seen in elderly patients when compared to younger patients who received the same dose. The reason for this is unclear, but is most likely related decreased renal function in the older population.

Gabapentin is a renally excreted medication. Therefore, the dosage of gabapentin must be adjusted in patients with renal insufficiency. No studies have been completed on patients younger than 12 years with renal insufficiency. Recommended dosage adjustment for patients aged 12 and older with renal impairment is as follows: for patients with creatinine clearance (CrCl) greater than or equal to 60 mL/min, total daily gabapentin dosing range is 900–3,600 mg/day administered three times a day. For patients with CrCl ranging from greater than 30 to 59 mL/min, total daily gabapentin dosing range is 400–1,400 mg/day administered two times a day. For patients with CrCl ranging from greater than 15 to 29 mL/min, total daily gabapentin dosing range is 200–700 mg/day administered in a single daily dose. For patients with CrCl of 15 mL/min, total daily gabapentin dosing range is 100–300 mg/day administered in a single daily dose. In patients whose CrCl is below 15 mL/min, gabapentin can be used; however, these patients should receive a single daily dose that is decreased in proportion to the decrease in their CrCl below 15 mL/min. For example, a patient with CrCl of 7.5 mL/min should receive a single daily dose of gabapentin that is one-half the amount of the single daily dose of the patient whose CrCl is 15 mL/min. Furthermore, patients on hemodialysis require an additional posthemodialysis supplemental dose ranging between 125 and 350 mg/dose. As gabapentin is not known to be metabolized hepatically, no studies have been performed in patients with hepatic insufficiency.

### Pediatric Use

Gabapentin is indicated in children aged 3 or older as adjunctive therapy in the treatment of partial seizures with and without secondary generalization (29,20). Recommended initial dose is 10–15 mg/kg/day in three divided doses. Gabapentin can be quickly titrated up to target dosing over the course of approximately 3 days. Target dosing for patients aged 3 and 4 years is 40 mg/kg/day in three divided doses. Target dosing for patients aged 5 years and older is 25–35 mg/kg/day in three divided doses. Doses up to 50 mg/kg/day have been tolerated in a variety of pediatric age groups. Maximum interval between doses should not be greater than 12 hours.

## TOPIRAMATE

### Indications

Topiramate is indicated as initial monotherapy for partial-onset or primary generalized tonic-clonic seizures in patients

2 years and older, as adjunctive therapy for partial-onset or primary generalized tonic-clonic seizures in patients 2 years or older, and as adjunctive therapy in patients over age two who have seizures associated with Lennox-Gastaut syndrome (31).

### Dosing

When topiramate is used as monotherapy for epilepsy in patients 10 years or older, the recommended dose is 400 mg/day divided in two doses. To reach this target dose, topiramate should be titrated. Typically, topiramate is started at 25 mg twice daily and is increased by 25 mg per dose each week for the first four weeks. Subsequently, the dose may be increased by 50 mg per dose so that the target dose of 400 mg/day is achieved in 6 weeks. When topiramate is used as an adjunctive therapy in patients with partial-onset seizures, the recommended dosing is 200 mg/day to 400 mg/day in two divided doses. In patients being treated for primary generalized tonic-clonic seizures, topiramate is recommended at 400 mg/day in two divided doses for adjunctive therapy. Titration of topiramate is still recommended when topiramate is used as an adjunctive medication. Typical titration includes initiation at 25 to 50 mg/day followed by increases of 25 to 50 mg/day every week. Topiramate is only available in tablets and capsules. A once-a-day oral extended-release preparation has recently become available. Some pharmacies compound topiramate as a 6 mg/ml solution. There is no intravenous form.

### Pharmacology

A definitive mechanism of action of topiramate is not known. In studies, topiramate has been noted to block voltage-dependent sodium channels, to antagonize the glutamate receptor at the AMPA-kainate subtype of the receptor, to augment the activity of GABA at some subtypes of the GABA-A receptor, and to inhibit particular isozymes of the carbonic anhydrase enzyme.

Following a 400 mg dose, peak plasma concentrations of topiramate occur in approximately 2 hours. Food does not affect the bioavailability of topiramate. Topiramate has linear pharmacokinetics with increases in medication dosing leading to proportional increases in plasma concentrations. The half-life for elimination of topiramate is 21 hours, meaning that steady state is reached in approximately 4 days in a patient with normal renal function. Interestingly, topiramate is minimally metabolized. It is eliminated in the urine largely unchanged.

### Efficacy Data

The efficacy of topiramate as an initial monotherapy for partial seizures or primary generalized tonic-clonic seizures was evaluated in a trial in which enrollees were randomized

to receive either 50 mg/day or 400 mg/day of topiramate. The 400 mg/day group had a statistically longer time to first seizure regardless of baseline seizure type than the 50 mg/day group. Topiramate in children age 2 to 10 years as initial monotherapy for partial seizures or primary generalized tonic-clonic seizures has been shown to produce a similar response as in adults. Dosing recommendations in this population were derived from simulations based on pediatric and adult plasma exposure ranges when topiramate is used as initial monotherapy.

Multiple trials have demonstrated the efficacy of topiramate as an adjunctive therapy for partial seizures in adults, for partial seizures in children aged 2 to 16, and for primary generalized tonic-clonic seizures in patients aged 2 and older in trials evaluating frequency of seizures compared to baseline when taking topiramate versus placebo. These trials have shown a statistically significant benefit of topiramate over placebo as an adjunctive antiepileptic medication in partial and generalized tonic-clonic seizures.

The efficacy of topiramate has also been evaluated as an adjunctive medication for seizures in Lennox-Gastaut syndrome and was studied in patients aged 2 and older. Primary efficacy measures were the percent reduction in drop attacks and a parental rating of seizure severity. Using these measures topiramate was found to be effective in the previously mentioned patient population.

### Efficacy in Other Conditions

In addition to uses in epilepsy, topiramate is indicated for migraine prophylaxis but not for treatment of acute migraine exacerbation (32). Non-FDA-approved uses in neurology reported in the literature include treatment for idiopathic intracranial hypertension, essential tremor, and neuropathic pain (33–35). Topiramate has been tried in a variety of psychiatric disorders mentioned in the following with mixed results but is not currently FDA approved for use in any psychiatric illness (36). Topiramate has been tried in bipolar disorder for mania, depression, rapid-cycling, and treatment-refractory; in unipolar depression; in schizophrenia, schizoaffective disorders, and other psychosis; in eating disorders; in post-traumatic stress disorder; in alcohol dependence; in borderline personality disorder; and in Tourette's syndrome (37). Topiramate has also been studied as a weight loss agent (38).

### Adverse Effects

The most common adverse reactions reported in clinical trials of topiramate in epilepsy include paresthesias, anorexia and resulting weight loss, fatigue, dizziness, psychomotor slowing, cognitive problems, difficulty with concentration, difficulty with memory, nervousness, confusion, mood problems, infection, fever, and flushing. More severe, but less common, adverse effects are discussed in the following Warnings and Precautions section.

### Toxicity, Overdose, and Contraindications

Overdose on topiramate has been reported. While the majority of overdoses were not clinically severe, deaths have been reported when topiramate overdose occurs in combination with overdose on other medications. As expected, topiramate overdose may result in severe metabolic acidosis. Coma, lethargy, status epilepticus, cognitive slowing, changes in speech, diplopia, blurred vision, dizziness, difficulty with coordination, hypotension, abdominal pain, and depression have all been reported in topiramate overdose cases. Topiramate overdose may be managed by gastric lavage or induction of emesis if recent. In laboratory studies, topiramate has been effectively absorbed by activated charcoal. Hemodialysis is effective in removing topiramate, but should be reserved for severe symptoms. Treatment is largely supportive. Bicarbonate may be needed for treatment of severe metabolic acidosis. No specific antidote exists for use in topiramate overdose or toxicity (11). There are no definite contraindications to the use of topiramate; however, caution should be used in patients with certain preexisting conditions as discussed later.

### Warnings and Precautions

Topiramate has been associated with the development or exacerbation of several significant medical conditions. A syndrome of acute myopia and secondary angle closure glaucoma has been reported with topiramate in both adult and pediatric patients and is usually seen within the first month after initiation of the medication. Decreased sweating and, rarely, hyperthermia has been cited in patients using topiramate. This has been reported more frequently in the pediatric population and severe hyperthermia has typically been in the setting of concomitantly elevated environmental temperatures (39).

Hyperchloremic metabolic acidosis without an anion gap is a known effect of topiramate and is related to the increase in renal bicarbonate loss that results from topiramate's inhibition of carbonic anhydrase. Metabolic acidosis related to topiramate typically develops early in treatment and is usually mild to moderate. Manifestations of severe, untreated, acute, or chronic metabolic acidosis include hyperventilation, anorexia, fatigue, cardiac arrhythmias, or stupor. Chronic, untreated severe metabolic acidosis may also increase the risk for nephrocalcinosis or nephrolithiasis and may result in osteomalacia, termed rickets in pediatric populations, or osteoporosis. Consequently, pediatric patients suffering from chronic metabolic acidosis may experience decrease in growth rates that may theoretically lead to decrease in final height. It is also important to note that metabolic acidosis may affect fetuses of pregnant patients taking topiramate.

Topiramate, like all antiepileptic medications, may increase suicidal thought or suicidal behavior. Increase in

suicidal thoughts usually occur within 1 week of starting the medication and persist until discontinuation of the antiepileptic drug in question.

Cognitive and neuropsychiatric side effects were one of the most frequently reported adverse events in studies. These included cognitive slowing, difficulty with attention or concentration, difficulty with speech or language, behavioral or psychiatric disturbances, and fatigue or somnolence. The majority of these side effects was mild to moderate in severity and was worse in patients who underwent rapid titration or higher doses of topiramate.

As discussed in detail in the teratogenicity section, topiramate is a Pregnancy Category D medication and should be used in pregnancy only when benefit significantly outweighs risk. Just as topiramate should be titrated for initiation of therapy, it should also be tapered off when discontinuing therapy as abrupt discontinuation may increase the risk for seizures or may increase seizure frequency.

Initial studies of patients taking topiramate did identify SUDEP at a higher incidence than in healthy patients matched for sex and age. However, the incidence of SUDEP in patients taking topiramate was not significantly higher than in patients with epilepsy who were not taking topiramate.

Use of topiramate has been associated with hyperammonemia with and without accompanying encephalopathy. This risk is increased in patients receiving topiramate and valproate concomitantly, and this adverse effect is more common in the pediatric population. In addition, the use of topiramate and valproate together has been associated with hypothermia both in the presence and in the absence of hyperammonemia. Use of topiramate is correlated with an increased risk of nephrolithiasis in the adult and pediatric populations and is likely related to the carbonic anhydrase inhibitory properties of topiramate. Concomitant use of other medications that cause metabolic acidosis and potentially the concomitant use of the ketogenic diet may increase the likelihood of nephrolithiasis. Good hydration should be recommended to minimize this potential complication. Paresthesias, usually consisting of tingling in the extremities, were a commonly reported side effect in studies of topiramate but rarely led to discontinuation of the medication.

### Teratogenicity

Topiramate is a Pregnancy Category D medication. Increased risk of cleft lip and cleft palate has been noted in neonates of pregnant patients who took topiramate during pregnancy. In addition, hypospadias and rare cardiovascular anomalies have been seen. No apparent dose effect has been appreciated between patients who were born with congenital defects and those who were not (12). In addition, while the effects of metabolic acidosis on fetuses related to topiramate use have not been studied, metabolic acidosis from other causes has been associated with decreased fetal growth, decreased fetal



oxygenation, decreased fetal ability to tolerate labor, and even fetal death.

### Special Safety Concerns and Monitoring

Monitoring topiramate levels is usually not necessary. Given the possibility of development of hyperchloremic, nongap, metabolic acidosis while on topiramate therapy, measurement of baseline and periodic bicarbonate levels is recommended. In addition, some studies of patients taking topiramate as an adjunctive therapy for epilepsy have shown a significant decrease in serum phosphorus, a decrease in serum potassium, and a significant increase in serum alkaline phosphatase, although the significance of these findings has not been established. Increase in total protein, increase in creatinine, and increase in BUN have also been observed. As previously discussed, topiramate can produce hyperammonemia both with and without encephalopathy. While no formal recommendations exist regarding the frequency of monitoring for this complication, checking of baseline and periodic ammonia levels should be considered.

### Drug Interactions

Topiramate has several possible drug–drug interactions that must be considered, including interactions with other antiepileptic medications. When topiramate is administered concomitantly with carbamazepine or phenytoin in studies, topiramate levels are reduced by up to 40% or 48%, respectively. Coadministration of topiramate and valproic acid has been associated with elevated ammonia levels with and without accompanying encephalopathy as well as hypothermia with and without accompanying hyperammonemia. Coadministration of topiramate with lamotrigine may result in slightly decreased levels of topiramate. The use of topiramate with other CNS depressant medications or alcohol has not been fully studied, but potential interactions between topiramate and these medications are concerning given the association of topiramate use with CNS depression and cognitive difficulties.

Some studies have demonstrated decreased efficacy of oral contraceptives when used concomitantly with topiramate, and patients should be aware of this possibility. Furthermore, lithium levels may be affected by coadministration of high-dose topiramate. While studies have shown no change in lithium levels with topiramate doses of 200 mg/day, lithium levels have been noted to increase when patients were concomitantly taking doses of topiramate up to 600 mg/day. Given the well-known side effect of metabolic acidosis associated with topiramate use, patients taking topiramate should not also be taking metformin, as the use of metformin is contraindicated in the setting of metabolic acidosis. Likewise, topiramate, which causes metabolic acidosis via its mechanism as a carbonic anhydrase inhibitor,

should not be prescribed concomitantly with other carbonic anhydrase inhibitors as this may increase the likelihood of developing severe metabolic acidosis and of developing kidney stones.

### Use in Special Populations

Topiramate-induced metabolic acidosis may also occur and may be significant for a pregnant or laboring patient and her fetus although the effects of topiramate during labor and delivery have not been studied in detail. Similarly, the use of topiramate in a breast-feeding mother has not been fully studied. Topiramate has been found in the plasma of neonates breast-fed by mothers taking this medication. However, infant plasma levels of topiramate were significantly lower than maternal plasma levels in these cases.

While patients over the age of 60 have been studied in topiramate trials without observation of age-related difference in efficacy or in likelihood of adverse effects, the number of older patients involved in these trials was insufficient to conclude whether or not elderly populations respond differently to topiramate than younger populations.

The clearance of topiramate is decreased in patients with renal impairment. In patients with moderate or severe renal impairment, one-half of the usual starting dose and maintenance dose is recommended. Similarly, patients undergoing dialysis require supplemental doses of topiramate given increased clearance of the medication; however, exact dosage of supplementation depends on details related to the patient and the dialysis. The clearance of topiramate may be decreased in patients with hepatic impairment as well, but the mechanism by which hepatic impairment decreases clearance is not well understood.

### Pediatric Use

Topiramate is approved for use as a monotherapy or an adjunctive therapy in partial-onset or primary generalized tonic-clonic seizures in patients aged 2 and older. Topiramate is also indicated as an adjunctive medication for patients aged 2 and older with Lennox-Gastaut syndrome-associated seizures. Topiramate has been utilized in the treatment of infantile spasms as well (16). For children aged 2 to 10, a weight-based dosing approach is used for topiramate when prescribed as a monotherapy for partial-onset or for generalized tonic-clonic seizures. Titration is recommended. The initial starting dose for this age group is 25 mg/day administered at night for the first week. During the second week, this may be increased to 50 mg/day. Dosage can be increased by 25 mg/day to 50 mg/day each week during subsequent weeks as tolerated by the patient. The following minimum target doses for efficacy and maximum target doses for tolerability have been recommended based on weight: for children 11 kg or less, minimum dose of 150 mg/day and

maximum dose of 250 mg/day; for children 12 kg to 22 kg, minimum dose of 200 mg/day and maximum dose of 300 mg/day; for children 23 kg to 31 kg, minimum dose of 200 mg/day and maximum dose of 350 mg/day; for children 32 kg to 38 kg, minimum dose of 250 mg/day and maximum dose of 350 mg/day; and for children weighing more than 38 kg, minimum dose of 250 mg/day and maximum dose of 400 mg/day. Doses should be given in two equally divided doses each day. For patients aged 10 years or older, recommended dosing for topiramate used as a monotherapy for partial-onset or for generalized tonic-clonic seizures is the same as for adults as described earlier with a maximum dose of 400 mg/day in two divided doses.

When topiramate is used as an adjunctive therapy for partial-onset, primary generalized tonic-clonic seizures, or for seizures associated with Lennox-Gastaut syndrome, dosing is weight based for children aged 2 to 16. The recommended total daily dose of topiramate is 5 mg/kg/day to 9 mg/kg/day in two equally divided doses. Topiramate should be initiated with a dose between 1 mg/kg/day and 3 mg/kg/day as a single nightly dose for the first week. The dose can then be safely increased by 1–3 mg/kg/day every 1 to 2 weeks. After the initial week, topiramate should be given in two, equal divided doses. Dosing for patients aged 17 and older for topiramate used as an adjunctive therapy for partial-onset, primary generalized tonic-clonic seizures, or for seizures associated with Lennox-Gastaut syndrome is the same as for adults and is described previously in the section on dosing.

## LEVETIRACETAM

### Indications

Levetiracetam is indicated as adjunctive treatment of (a) partial-onset seizures in adults and children 4 years of age and older with epilepsy; (b) myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy; and (c) primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy (40). There is also some evidence that levetiracetam may be useful in the treatment of infantile spasms (41).

### Dosing

In adults and children older than 16 years treatment is started at 1,000 mg/day and given as twice-daily dosing. Dose can be increased by 1,000 mg/day every 2 weeks to a maximum of 3,000 mg/day. When switching from oral levetiracetam to IV form, the initial total daily intravenous dosage of levetiracetam should be equivalent to the total daily dosage and frequency of oral levetiracetam and vice versa. Levetiracetam is available as 250 mg, 500 mg, 750 mg and 1,000 mg tablets and also in liquid form (100 mg/mL) for oral administration. It is also available in IV form as a single

use vial with 500 mg/5mL (100 mg/mL) strength. Extended release tablets, for once/day dosing, are available.

## Pharmacology

Levetiracetam binds to the SV2A synaptic vesicle glycoprotein and is thus thought to interfere in neurotransmitter release and synaptic transmission. It is also thought to inhibit presynaptic calcium channels and to enhance GABAergic inhibition.

Levetiracetam is quickly absorbed and has 100% bioavailability when taken orally. The tablets and oral solution are bioequivalent. Pharmacokinetics are linear with no time-variance and low intra- or inter-subject variability. Food does not affect bioavailability of levetiracetam. Only less than 10% of levetiracetam is protein-bound and its volume of distribution is close to the volume of intracellular and extracellular water. Majority of the dose (66%) is renally excreted unchanged. The major metabolic pathway of levetiracetam is an enzymatic hydrolysis of the acetamide group, which is not liver cytochrome P450 dependent. The metabolites do not have known pharmacological activity and are also renally excreted. Peak plasma concentrations occur in an hour and plasma half-life is approximately 6 to 8 hours, but can be increased in the elderly and in patients with renal impairment.

## Efficacy

The effectiveness of levetiracetam as adjunctive therapy in adults with refractory partial-onset seizures with or without secondary generalization was established in three multicenter, randomized, double-blind, placebo-controlled clinical studies. All three studies showed statistically significant response (defined as  $\geq 50\%$  reduction from baseline) to levetiracetam when compared to placebo. The efficacy of levetiracetam as adjunctive therapy in patients 12 years of age and older with juvenile myoclonic epilepsy experiencing myoclonic seizures was established in one multicenter, randomized, double-blind, placebo-controlled study that was conducted at 37 different sites across 14 countries. The levetiracetam group showed 60.4% response as opposed to 23.7% in the placebo group.

To study the efficacy of levetiracetam as adjunctive therapy in pediatric patients (aged 4–16 years) with partial seizures refractory to standard AEDs, a randomized double-blind, placebo-controlled study was conducted at 60 different sites in North America. It showed 26.8% reduction in partial seizure frequency over placebo. In children aged 1 month to 4 years with refractory partial seizures a multicenter, randomized double-blind, placebo-controlled study was conducted at 62 different sites spanning across North America, South America, and Europe. The primary measure of effectiveness was the percentage of patients with a greater than or equal to 50% reduction from baseline in average daily partial-onset seizure frequency assessed by a

blinded central reader using a 48-hour video EEG. Levetiracetam group showed a 43.1% response whereas it was only 19.6% in placebo group.

The effectiveness of levetiracetam as an adjunctive therapy in patients 6 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic (PGTC) seizures was established in one multicenter, randomized, double-blind, placebo-controlled study, conducted at 50 sites in 8 countries. There was a 77.6% reduction in baseline seizure frequency per week in patients treated with Levetiracetam as compared to a 44.6% reduction in the placebo group.

### Efficacy in Other Conditions

Levetiracetam has been reported as efficacious in various forms of myoclonus. These include posthypoxic myoclonus, postencephalitic myoclonus, Unverricht-Lundborg disease myoclonus, progressive myoclonic epilepsy, spinal myoclonus, paraneoplastic myoclonus, and myoclonus dystonia (42–46). However, one open-label trial that used levetiracetam for myoclonus of various etiologies that had previously been refractory to at least one treatment showed highly inconsistent responses to levetiracetam. Responses ranged from dramatic improvement to no improvement. The degree of response did not seem to correlate with the etiology of the myoclonus (47).

### Adverse Effects

Levetiracetam use has been associated with the occurrence of central nervous system side effects that can be classified into the following categories: (a) somnolence and fatigue, (b) coordination difficulties, and (c) behavioral abnormalities. Behavior abnormalities are described as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis, and personality disorder. Pyridoxine, usually at 100 mg/day, has been reported to help reduce the hyperkinesia and hostility side effects.

### Toxicity, Overdose, and Contraindications

During the clinical developmental program, the highest known dose of levetiracetam received was 6,000 mg/day. Drowsiness was the only adverse effect reported in the few cases of overdose in other clinical trials. However, in post-marketing use somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma have been observed with levetiracetam overdoses (48). Levetiracetam does not have a specific antidote. In cases of overdose, the usual precautions to maintain airway should be taken and if required elimination of unabsorbed drug can be attempted with emesis or gastric lavage. General supportive care should also be given to the patient. Standard

hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. To date, hemodialysis has not been used in the few known cases of overdose. However, it may be indicated in certain patients due to their clinical state or degree of renal impairment.

### Warnings and Precautions

Levetiracetam should not be prescribed to patients who have previously exhibited hypersensitivity to it or to any of its inactive ingredients. Levetiracetam like other AEDs can increase the risk of suicidal thoughts or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs (including levetiracetam) showed that patients taking any one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% CI 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. Therefore, patients should be monitored closely for changes in mood or behavior and emergence of depression.

### Teratogenicity

Levetiracetam is a Pregnancy Category C drug. There have been no adequate and well-controlled studies conducted in pregnant women. Animal studies have shown evidence of developmental toxicity, including teratogenic effects, at doses similar to or greater than human therapeutic doses. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant patients who took levetiracetam were enrolled in the AED pregnancy registry. As much as 2.4% of the neonates studied were born with congenital anomalies. The most common anomalies were cardiovascular anomalies and neural tube defects that were equally common. Oral clefting and hypospadias were not observed (12).

### Special Safety Concerns and Monitoring

Behavioral side effects in children and depression in adults can occur in some patients. Blood levels are mostly useful for checking of compliance and to a lesser extent, if any, for predicting efficacy.

### Drug Interactions

In vitro data on metabolic interactions indicate that levetiracetam is not likely to produce or be subjected to pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C<sub>max</sub> levels achieved within the therapeutic dose range, neither inhibits nor has high affinity substrates for human liver cytochrome P450 isoforms. Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; therefore, clinically significant interactions

with other drugs through competition for protein binding sites are unlikely.

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic for following drugs:

### *Phenytoin*

Levetiracetam (3,000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam was also not affected by phenytoin. Levetiracetam (1,500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate (500 mg twice daily) did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion.

Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, and primidone) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. The data from these studies indicated that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

There was about a 22% increase of apparent total body clearance of levetiracetam when it was coadministered with enzyme-inducing AEDs. However, dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

### *Other Drug Interactions*

Oral contraceptives, digoxin, warfarin, and probenacid were studied and none of these drugs was found to alter the pharmacokinetics of levetiracetam. Moreover, coadministration of levetiracetam did not influence the pharmacokinetics or pharmacodynamics of these drugs either.

### **Use in Special Populations**

Pharmacokinetics of levetiracetam was studied in 16 elderly subjects between ages 61 and 88 years whose creatinine clearance ranged from 30 to 74 mL/min. Following oral administration of twice-daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Levetiracetam levels may decrease during pregnancy. The disposition of levetiracetam was studied in adult subjects with varying degrees of renal function. Total body clearance of levetiracetam was reduced in patients with impaired renal function by 40% in the mild group (Creatinine clearance rate or CLcr = 50–80 mL/min), 50% in the moderate group (CLcr = 30–50 mL/min), and 60% in the severe renal impairment group (CLcr <30 mL/min). Clearance of levetiracetam is directly correlated with CLcr. In anuric (end-stage

renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLcr >80 mL/min). About 50% of the pool of levetiracetam in the body can be removed during a standard 4-hour hemodialysis procedure. Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis.

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. Therefore, no dose adjustment is needed for patients with hepatic impairment.

Levetiracetam is excreted in human milk. Because of the potential for serious adverse reactions from levetiracetam in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug.

### **Pediatric Use**

Levetiracetam is indicated for adjunctive therapy in the treatment of (a) partial-onset seizures in patients one month of age and older with epilepsy, (b) myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and (c) primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy. For children aged 4 to 16 years, levetiracetam is started at 20 mg/kg/day, which is given in two divided doses. The daily dose is increased every 2 weeks by 20 mg/kg/day to the recommended 60 mg/kg/day. Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6–12 years) after single dose (20 mg/kg). The body weight-adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults. Following single-dose administration (20 mg/kg) of a 10% oral solution to children with epilepsy (1 month to < 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 mL/min/kg) than for adults (0.96 mL/min/kg). Population pharmacokinetic analysis showed that body weight was significantly correlated to the clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

## **OXCARBAZEPINE (OXC)**

### **Indications**

Oxcarbazepine is used as monotherapy or adjunctive therapy in the treatment of partial seizures in adults. For children, it is indicated as monotherapy in the treatment of partial seizures in children older than 4 years of age with epilepsy and as an adjunctive therapy in children older than 2 years (49).



## Dosing

When used as adjunctive treatment, oxcarbazepine is initiated with a dose of 600 mg/day, which is given in a twice-daily regimen. If required, the dose can be increased by a maximum of 600 mg/day at 1-week intervals. Per FDA guidelines, the recommended daily dose for adjunctive therapy is 1,200 mg/day. Even though controlled trials have demonstrated greater effectiveness of daily doses above 1,200 mg/day, most patients were unable to tolerate the 2,400 mg/day dose due to side effects of central nervous system and increased interaction with other AEDs.

Patients who are currently receiving other AEDs can be converted to monotherapy by initiating treatment with oxcarbazepine at 600 mg/day (given in a twice-a-day regimen) while simultaneously reducing the dose of the concomitant AEDs. These AEDs should ideally be completely withdrawn over 3 to 6 weeks, while the maximum dose 2,400 mg/day of oxcarbazepine should be achieved in about 2 to 4 weeks. Patients should be closely monitored during the transition.

In patients not receiving other AEDs (monotherapy use), oxcarbazepine is initiated at a dose of 600 mg/day (given in a twice-a-day regimen); the dose is increased by 300 mg/day every third day to a dose of 1,200 mg/day. The maximum dose of 2,400 mg/day is reserved for patients switched to oxcarbazepine from other AEDs. All dosing should be given in a twice-a-day regimen. Oxcarbazepine oral suspension and oxcarbazepine film-coated tablets are interchangeable at equal doses. Oxcarbazepine is available in 150, 300, and 600 mg tablets and 300 mg/5 ml suspension (Trileptal). Similar size extended-release tablets (Oxtellar) for once/day use that need to be given either at least one hour before or two hours after meals are also available.

## Pharmacology

The exact mechanism of action is unknown. In vitro electrophysiological studies indicate that oxcarbazepine blocks voltage-sensitive sodium channels causing inhibition of repetitive neuronal firing, decreasing propagation of synaptic impulses, and stabilizing hyper-excited neural membranes.

Oxcarbazepine is completely absorbed after oral administration and is metabolized to its pharmacologically active form 10-monohydroxy metabolite (MHD). The half-life of oxcarbazepine is about two hours, while the half-life of MHD is about nine hours, so MHD is responsible for most antiepileptic activity. Food does not affect rate and extent of absorption of oxcarbazepine. Therefore, the tablets and suspension can be taken with or without food. Twice-a-day dosing of oxcarbazepine allows steady-state plasma concentrations of MHD to be reached within 2 to 3 days. It is excreted by the kidneys and greater than 95% of the dose appears in the urine.

## Efficacy Data

Four randomized, controlled, double-blind, multicenter trials were conducted in the adult population to prove the efficacy of oxcarbazepine as monotherapy. All studies showed statistically significant results in favor of oxcarbazepine compared with placebo. To establish the effectiveness of oxcarbazepine, as an adjunctive therapy for partial seizures, two multicenter, randomized, double-blind, placebo-controlled trials were conducted. One study had 692 patients (15–66 years of age) and the other 264 pediatric patients (3–17 years of age). The comparison was statistically significant in favor of oxcarbazepine at all doses tested in both trials. However, over 65% of patients in the high-dose (2400 mg/day) treatment group discontinued treatment because of adverse effects on cognition that was not seen in the monotherapy studies. Another rater-blind, randomized, age-stratified, parallel-group study was done comparing two doses of oxcarbazepine in 128 pediatric patients (1 month to < 4 years of age). The comparison was statistically significant in favor of oxcarbazepine (60 mg/kg/day) compared with placebo. However, in this study, there was no evidence that oxcarbazepine was effective in patients below the age of 2 years. The efficacy of oxcarbazepine and carbamazepine has been compared as well and is similar (50).

## Efficacy in Other Conditions

Uses for oxcarbazepine reported in the literature but not FDA approved include bipolar disorder, panic disorder, and agitation (51). Recent studies have not substantiated oxcarbazepine as more efficacious than placebo in the treatment of bipolar disease in children however (52). In addition, no significant effect of oxcarbazepine on agitation and aggression in severe dementia has been substantiated (53). There is some evidence that oxcarbazepine can be efficacious in the treatment of neuropathic pain (54).

## Adverse Effects

The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in association with oxcarbazepine were dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait. Pediatric patients also reported similar adverse effects as the adult population. About 11% of 456 pediatric discontinued treatment because of somnolence (2.4%), vomiting (2.0%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), and nystagmus (1.1%).

## Toxicity, Overdose, and Contraindications

Oxcarbazepine should not be used in patients with a known hypersensitivity to it or to any of its components. Isolated cases of overdose have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered

with symptomatic treatment. There is no specific antidote. Treatment is symptomatic and supportive.

### Warnings and Precautions

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine, the drug should be discontinued and an alternative treatment started. Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. Like other antiepileptic drugs, oxcarbazepine increases the risk of suicidal thoughts or behavior in patients. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Lastly, patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of them might experience hypersensitivity reactions with oxcarbazepine. One case has been reported that raised concern that oxcarbazepine therapy may induce infantile spasms and West syndrome (55). Likewise, worsening of myoclonus in juvenile myoclonic epilepsy and myoclonic status epilepticus, concerns traditionally raised with administration of carbamazepine, have been reported with oxcarbazepine (56).

### Teratogenicity

While small numbers of neonates born to patients taking oxcarbazepine were enrolled in the AED pregnancy registry, the numbers were not sufficient to draw conclusions as to the possible congenital anomalies related to this drug. It is a Pregnancy Category C drug as increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity were observed in the offspring of animals treated with either oxcarbazepine or MHD during pregnancy at doses similar to the maximum recommended human dose (12).

### Special Safety Concern and Monitoring

Clinically significant hyponatremia (sodium  $<125$  mmol/L) can develop during oxcarbazepine use. Measurement of serum sodium levels should be considered for patients during maintenance treatment with oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels or if symptoms possibly indicating hyponatremia develop such as nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity.

### Drug Interactions

Carbamazepine, phenytoin, and phenobarbital are strong inducers of cytochrome P450 and have been shown to decrease the plasma levels of MHD up to 29% to 40%. Concurrent use of oxcarbazepine with hormonal contraceptives may render contraceptives less effective as oxcarbazepine decreases levels of ethinylestradiol and levonorgestrel. Verapamil has been shown to decrease plasma levels of MHD by 20%. Oxcarbazepine appears to increase concentrations of phenytoin and to decrease trough concentrations of lamotrigine and topiramate, because oxcarbazepine has absent or lower enzyme-inducing effects, switching from carbamazepine to oxcarbazepine can result in increased serum concentrations of background medications.

### Use in Special Populations

Mild-to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine has not been evaluated in severe hepatic impairment, and, therefore, caution should be exercised when dosing severely impaired patients.

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300-mg dose in renally-impaired patients (creatinine clearance  $<30$  mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two-fold increase in area under the curve (AUC). Dose adjustment for oxcarbazepine is recommended in these patients.

Oxcarbazepine and its active metabolite are excreted in breast milk. Therefore, the risks and benefits of the use of this medication in nursing mothers should be carefully considered.

### Pediatric Use

When used as adjunctive therapy in pediatric patients aged 4 to 16 years, oxcarbazepine should be initiated at a daily dose of 8–10 mg/kg generally not to exceed 600 mg/day, given in a twice-a-day regimen. The target maintenance dose of oxcarbazepine should be achieved over 2 weeks, and is dependent upon patient weight, according to the following chart schedule: 20 to 29 kg, 900 mg/day; 29.1 to 39 kg, 1,200 mg/day;  $>39$  kg, 1,800 mg/day. In pediatric patients aged 2 to less than 4 years, treatment should also be initiated at a daily dose of 8 to 10 mg/kg, generally not to exceed 600 mg/day, given in twice-a-day regimen. For patients less than 20 kg, a starting dose of 16–20 mg/kg may be considered. The maximum maintenance dose of oxcarbazepine should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day in a twice-a-day regimen. Under adjunctive therapy apparent clearance (L/hr/kg) decreased when age increased such that children 2 to less than 4 years of age may require up to twice the oxcarbazepine dose per

body weight compared to adults; and children 4 to less than or equal to 12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults.

Children aged 4 to 16 years receiving concomitant antiepileptic drugs may be converted to monotherapy of oxcarbazepine by initiating treatment at approximately 8 to 10 mg/kg/day given in a twice-a-day regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks, while oxcarbazepine may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase

## TIAGABINE

### Indications

Tiagabine is approved as adjunctive therapy in the treatment of partial seizures in patients aged 12 and older (57,58).

### Dosing

Tiagabine is an oral medication that should be administered with food. The initiation of tiagabine requires titration over several weeks. As the plasma concentration of tiagabine is significantly affected by hepatic enzyme-inducing medications, the dosing of tiagabine is dependent upon whether or not a patient is taking inducing medications concomitantly. In patients aged 12 and older who are taking enzyme-inducing antiepileptic medications at the time of initiation of tiagabine, a starting dose of 4 mg once daily should be used for 1 week. Following this, dose increases can be made once weekly according to the following titration. Increase tiagabine dose by 4 mg to a dose of 8 mg/day given in two divided doses in week 2. Increase tiagabine dose by 4 mg to a dose of 12 mg/day given in three divided doses in week 3. Increase tiagabine dose by 4 mg to a dose of 16 mg/day given in two to four divided doses in week 4. Increase tiagabine dose by 4 to 8 mg for a total dose of 20 to 24 mg/day given in two to four divided doses in week 5. Increase tiagabine dose by 4 to 8 mg for a total dose of 24 to 32 mg/day given in two to four divided doses in week 6. The dose of tiagabine should continue to be increased until clinical response is seen or until dose reaches 32 mg/day. For 12- to 18-year-olds, 32 mg/day given in two to four divided doses is considered maximum dosing although a few adolescents have tolerated higher doses. For patients over the age of 18, maintenance dosing can continue to be increased up to 56 mg/day given in two to four divided doses if needed. It is important to note that in patients who are not taking enzyme-inducing AEDs the plasma concentration of tiagabine is estimated to be more than twice that of the concentration in patients who are taking enzyme-inducing AEDs. Therefore, patients who are not taking enzyme-inducing AEDs at the time of initiation of tiagabine require lower doses and may require

slower titration of tiagabine. At this time, tiagabine has been administered primarily to induced populations, and there are limited data on dosing in noninduced populations such that no official recommendations for titration exist.

### Pharmacology

The mechanism of action of tiagabine is not fully understood, but it is known that tiagabine enhances the activity of GABA. In vitro studies have shown that tiagabine blocks GABA uptake into presynaptic neurons by binding to sites associated with the GABA uptake carrier. This effectively increases the amount of GABA available for binding at sites on postsynaptic neurons (59).

Tiagabine is rapidly and nearly completely absorbed. Food does slow absorption rate but does not significantly alter the degree of absorption. Peak plasma concentration is reached in approximately 45 minutes when administered without food and in approximately 150 minutes when administered with food. Tiagabine was administered with food in all clinical trials. It exhibits linear pharmacokinetics. Notably, tiagabine is 96% bound to human plasma proteins. The metabolism of tiagabine is through the hepatic cytochrome P450 pathway. The half-life of tiagabine in healthy volunteers is 7 to 9 hours; however, tiagabine elimination is significantly affected in patients who are also receiving hepatic enzyme-inducing medications such that the clearance of tiagabine in induced patients is approximately 60% greater than in noninduced patients. The half-life of tiagabine in induced patients is 2 to 5 hours. Interestingly, studies on the steady-state values of tiagabine have shown diurnal variation with values being lower after the evening dose than after the morning dose.

### Efficacy Data

The efficacy of tiagabine was studied in three multicenter, double-blind, placebo-controlled, parallel-group, clinical trials involving 769 patients with refractory partial seizures who were taking at least one hepatic enzyme-inducing antiepileptic medication as well as in two placebo-controlled cross-over studies involving 90 patients completed in the United States and in Europe. The exact design of the placebo-controlled studies varied, but all studies included a titration phase and a fixed-dose phase. In study 1, patients were assessed on varying doses of tiagabine compared to placebo. In study two, patients were assessed on the same dose of tiagabine divided over two or four times per day dosing compared to placebo. In study three, patients were assessed on the same, three-times-a-day dosing of tiagabine compared to placebo. Patients in study 1 who were taking 32 mg/day of tiagabine or greater had a statistically significant median reduction in seizure frequency. Patients at lower doses also experienced reduction in seizure frequency, but the median reduction was not statistically significant. In addition, a dose-response relationship was appreciated in study 1 in which the proportion of patients who achieved a



particular level of reduction in the rates of all partial seizures was consistently higher at increased doses of tiagabine.

Study 2 demonstrated that in patients taking tiagabine, the proportion of patients achieving any particular level of reduction in the rate of all partial seizures was greater than in those taking placebo. However, only the patients in the group taking tiagabine four times a day were found to have a statistically significant median reduction and only in the frequency of complex partial seizures. Study 3 showed a statistically significant improvement in all partial and complex partial seizure rates in patients taking tiagabine compared to placebo. The two cross-over studies that assessed efficacy of tiagabine both showed statistically significant reductions in seizure rates in patients taking tiagabine over placebo.

### Efficacy in Other Conditions

Some open-label reports have suggested that the anticonvulsant tiagabine may be efficacious in bipolar disorder. There is a need to clarify the evidence available, in the form of randomized controlled trials, for its use in the treatment of acute affective episodes in bipolar disorder (60). Tiagabine has been used for anxiety and panic disorders. It did not show beneficial effects on clinical symptoms in panic disorder compared to placebo, but results of challenge experiments suggest that patients on tiagabine had decreased sensitivity to experimentally induced panic (61,62).

Tiagabine has been used for treatment of primary insomnia. One study showed that tiagabine increased slow-wave sleep and reduced wake after sleep onset in a dose-dependent manner. Tiagabine dosages up to 8 mg did not compromise next-morning alertness and psychomotor performance in adult patients with primary insomnia (63).

### Adverse Effects

Several side effects have been reported. The more frequent ones are classified according to type of system affected.

*General:* Allergic reaction, chest pain, chills, cyst, neck pain, and malaise. *Cardiovascular System:* Hypertension, palpitation, syncope, and tachycardia. *Digestive System:* Gingivitis and stomatitis. *Heme and Lymphatic System:* Lymphadenopathy. *Metabolic and Nutritional:* Edema, peripheral edema, weight gain, and weight loss. *Musculoskeletal System:* Arthralgia. *Nervous System:* Depersonalization, dysarthria, euphoria, hallucination, hyperkinesia, hypertonia, hyperesthesia, hypokinesia, hypotonia, migraine, myoclonus, paranoid reaction, personality disorder, hyporeflexia, stupor, twitching, and vertigo. *Respiratory System:* Bronchitis, dyspnea, epistaxis, and pneumonia. *Skin and Appendages:* Alopecia, dry skin, and sweating. *Senses:* Abnormal vision, ear pain, otitis media, and tinnitus. *Urogenital System:* Dysmenorrhea, dysuria, metrorrhagia, urinary incontinence, and vaginitis. The use of tiagabine has been reported with new onset of nonconvulsive status that can present as a

confusional state (64). It also can result in myoclonic seizures as an adverse effect.

### Toxicity, Overdose, and Contraindications

Tiagabine is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Human experience of acute overdose with tiagabine is limited. Eleven patients in clinical trials took single overdoses of tiagabine up to 800 mg. All patients fully recovered, usually within 1 day. The most common symptoms reported after overdose included somnolence, impaired consciousness, agitation, confusion, speech difficulty, hostility, depression, weakness, and myoclonus. One patient who ingested a single dose of 400 mg experienced generalized tonic-clonic status epilepticus, which responded to intravenous phenobarbital. From postmarketing experience, there have been no reports of fatal overdoses involving tiagabine alone (doses up to 720 mg). However, overdoses involving multiple drugs, including tiagabine, have often resulted in fatal outcomes. Symptoms most often accompanying tiagabine overdose, alone or in combination with other drugs, have included: seizures including status epilepticus in patients with and without underlying seizure disorders, nonconvulsive status epilepticus, coma, ataxia, confusion, somnolence, impaired speech, drowsiness, agitation, lethargy, myoclonus, tremors, spike wave stupor, disorientation, vomiting, hostility, and temporary paralysis. Respiratory depression was seen in a number of patients, including children, in the context of seizures. Management of Overdose: There is no specific antidote for overdose with tiagabine. Emesis or gastric lavage can be attempted to remove unabsorbed drug. Airway precautions should be taken and supportive care provided to the patient. Since tiagabine is mostly metabolized by the liver and is highly protein bound, dialysis is not useful.

### Warnings and Precautions

Postmarketing reports have shown that tiagabine use has been associated with new-onset seizures and status epilepticus in patients without epilepsy. Dose may be an important predisposing factor in the development of seizures, although seizures have been reported in patients taking daily doses of tiagabine as low as 4 mg/day. In most cases, patients were using concomitant medications (antidepressants, antipsychotics, stimulants, narcotics) that are thought to lower the seizure threshold. Some seizures occurred near the time of a dose increase, even after periods of prior stable dosing. In nonepileptic patients who develop seizures while on tiagabine treatment, tiagabine should be discontinued and patients should be evaluated for an underlying seizure disorder.

### Teratogenicity

Tiagabine is a Pregnancy Category C drug. While teratogenic effects were not seen in animal studies at doses



currently used in humans, a variety of malformations as well as decreased fetal weight were observed in animal studies when tiagabine was administered during early pregnancy at higher doses than currently prescribed to humans. Late pregnancy administration of high-dose tiagabine in animal studies resulted in decreased maternal weight gain, increased stillbirths, and decreased growth and survival of animals postnatally. The use of tiagabine in pregnancy should be avoided unless the benefit is felt to significantly outweigh risk.

### Special Safety Concern and Monitoring

A therapeutic range for tiagabine plasma concentrations has not been established. In controlled trials, trough plasma concentrations observed among patients randomized to doses of tiagabine that were statistically significantly more effective than placebo ranged from less than 1 ng/mL to 234 ng/mL (median, 10th, and 90th percentiles are 23.7 ng/mL, 5.4 ng/mL, and 69.8 ng/mL, respectively). Because of the potential for pharmacokinetic interactions between tiagabine and drugs that induce or inhibit hepatic metabolizing enzymes, it may be useful to obtain plasma levels of tiagabine before and after changes are made in the therapeutic regimen.

### Drug Interactions

Tiagabine is a nonenzyme-inducing medication. Studies of tiagabine administered concomitantly with other antiepileptic medications showed no effect on the concentrations of phenytoin or carbamazepine, showed a slight decrease in the concentration of valproate, and showed no significant change in the concentrations of phenobarbital or primidone, although further studies are needed. Studies investigating the effect of concomitantly administered antiepileptic medications on tiagabine showed an increase in tiagabine clearance of 60% in patients taking carbamazepine, phenytoin, phenobarbital, and/or primidone in combination with tiagabine. While no significant change was noted in the clearance or concentration of tiagabine when concomitantly administered with valproate in human subjects, *in vitro* studies have reported an increase of 40% in the free tiagabine concentration when valproate is administered with tiagabine. The clinical significance of this finding is unknown. The interactions of various other medications and tiagabine have been studied. No significant interactions were noted in the coadministration of tiagabine and cimetidine, theophylline, warfarin, digoxin, ethanol, triazolam, oral contraceptives, and antipyrine. Of note, *in vitro* studies have demonstrated that tiagabine is 96% bound to human plasma protein. Therefore, the potential for interaction of tiagabine with other highly protein bound medications exists.

### Use in Special Populations

Tiagabine administered in studies to geriatric patients showed similar pharmacokinetics as when administered to younger adults. Nonetheless, it is important to note that few geriatric patients were included in studies on tiagabine, and it is difficult to draw conclusions about the safety or efficacy of tiagabine in the geriatric population. As discussed previously, tiagabine is highly protein bound. Studies have shown that clearance of unbound tiagabine is significantly reduced in patients with moderate hepatic impairment. Thus, when compared to patients with normal hepatic function, patient with impaired hepatic function may require lower initial and maintenance doses and may require longer dosing intervals. Studies of tiagabine in patients with renal insufficiency have shown that the pharmacokinetics of bound and unbound tiagabine is not significantly affected in renal impairment even in renal failure necessitating hemodialysis. Therefore, no adjustment is needed to the dosing of tiagabine in patients with renal insufficiency.

### Pediatric Use

Tiagabine hydrochloride is indicated as adjunctive therapy in children 12 years and older in the treatment of partial seizures. Tiagabine has not been investigated adequately in well-controlled clinical trials in patients younger than 12 years of age. In adolescents 12 to 18 years old, tiagabine should be initiated at 4 mg once daily. Concomitant AEDs do not have to be modified, unless clinically indicated. The total daily dose of tiagabine may be increased by 4 mg at the beginning of week 2. Thereafter, the total daily dose may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day. The total daily dose should be given in divided doses two to four times daily.

Approval of felbamate in the early 1990s ushered in an era of many AED approvals. There is enough clinical experience with these drugs that many are used as monotherapy, regardless of whether that is an FDA-approved indication. Difficult lessons were learned as well. Unexpected side effects were noted with some of the medications (felbamate and tiagabine), which have greatly limited their use in routine settings. Most of these AEDs, however, were found to be well tolerated and at least as effective as traditional AEDs. The continued use of the second-generation AEDs will likely continue well into the future.

**Table 27.1 Summary of Second-Generation AEDs**

**Felbamate**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization in adults. In children with Lennox-Gastaut syndrome it can be used as adjunctive therapy for partial and generalized seizures.	1,200 mg/day in 3 to 4 divided doses. Increase by 600 mg/week.	2,400–3,600 mg/day	Start at 15 mg/kg/day and increase to 45 mg/kg/day.	Thought to act through enhancement of GABAergic and through anti NMDA receptor mechanism.	CNS: headache, insomnia, nervousness, somnolence. GI: dyspepsia, anorexia, hyperactivity, vomiting, diarrhea, constipation.	Category C	Increased risk of aplastic anemia, hepatic failure. Also known to cause suicidal ideation.	Increases valproate, phenytoin and phenobarbital levels and decreases carbamazepine levels. Its levels are decreased by enzyme inducers.

**Lamotrigine**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for partial seizures, primary generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older.	For patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, initiate 25 mg daily for weeks 1 and 2, increase to 50 mg daily for weeks 3 and 4, increase by 50 mg/day every one to two weeks to goal dosing	For patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, 225–375 mg/day divided in two equal doses	For patients not taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate, initiate 0.3 mg/kg/day in one or two divided doses for weeks 1 and 2, increase to 0.6 mg/kg/day in two divided doses for weeks 3 and 4, increase every 1 to 2 subsequent weeks by additional 0.6 mg/kg/day to goal dosing of 4.5 to 7.5 mg/kg/day with a maximum of 300 mg/day in two divided doses	Thought to block voltage-dependent sodium channels.	Headache, dizziness, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash in adult patients	Category C	Life-threatening rash, multiorgan hypersensitivity or DRESS syndrome, blood dyscrasias, aseptic meningitis, suicidality, increased frequency of seizure with abrupt discontinuation, SUDEP.	Interactions with other AEDs: phenobarbital, primidone, phenytoin, rifampin, carbamazepine decrease lamotrigine serum levels substantially; valproate significantly increases lamotrigine levels.
Monotherapy alternative in patients currently being treated with carbamazepine, phenytoin, phenobarbital, primidone, or valproate who are aged 16 or older.	For patients taking valproate, initiate 25 mg every other day for weeks 1 and 2, increase to 25 mg daily for weeks 3 and 4, increase by 25–50 mg/day every 1–2 weeks thereafter to goal dosing which varies based on concomitant AED use.  For patients continuing the inducing AEDs carbamazepine, phenytoin, phenobarbital, or primidone, initiate 50 mg/day for weeks 1 and 2, increase to 100 mg/day in two divided doses for weeks 3 and 4, increase by 100 mg/day every one to two subsequent weeks to goal dosing.	For patients also taking valproate but no inducing AED medications, 100–200 mg/day in one dose or two divided doses; for patients also taking the inhibitor valproate with inducing AED medications, 100–400 mg/day in one dose or two divided doses.  For patients continuing the inducing AEDs carbamazepine, phenytoin, phenobarbital, or primidone, goal dosing is 300–500 mg/day in two divided doses.	For patients also taking valproate, initiate at 0.15 mg/kg/day in one or two divided doses for weeks 1 and 2, increase to 0.3 mg/kg/day in weeks 3 and 4 in one or two divided doses, increase every 1 to 2 subsequent weeks by an additional 0.3 mg/kg/day to goal dosing. Goal dosing for patients taking valproate but no inducing AEDs 1–3 mg/kg/day divided into one or two divided doses. Goal dosing for patients taking valproate and other inducing AEDs is 1–5 mg/kg/day with a maximum of 200 mg/day in one or two divided doses; doses should be rounded down to the nearest whole tablet size.		Vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, tremor in pediatric patients.			Interactions with other medications: use with estrogen-containing birth control pills decreases lamotrigine levels and decreases OCP levels and effectiveness.

(continued)

**Table 27.1 Summary of Second-Generation AEDs (continued)**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
<p>For patients continuing carbamazepine, phenytoin, phenobarbital, or primidone but not valproate, initiate at 0.6 mg/kg/day in two divided doses for weeks 1 and 2, increase to 1.2 mg/kg/day in two divided doses for weeks 3 and 4, increase every subsequent 1 to 2 weeks by additional 1.2 mg/kg/day to goal dosing of 5–15 mg/kg/day with maximum of 400 mg/day in two divided doses.</p>								
<b>Gabapentin</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for partial seizures with or without secondary generalization in patients aged 3 or older.	Titrate to 900 mg/day in three divided days over a few days.	<p>Patients aged 12 and older: 900–1,800 mg/day in three divided doses.</p> <p>Maximum dosing 3,600 mg/day in three divided doses.</p>	<p>Patients aged 3–11: Initiate at 10–15 mg/kg/day in three divided doses with titration to goal dosing over a few days.</p> <p>Goal dosing:</p> <ul style="list-style-type: none"> <li>-aged 3 and 4 years: 40 mg/kg/day in three divided doses</li> <li>-aged 5 years and older: 25–35 mg/kg/day in three divided doses.</li> </ul> <p>Maximum pediatric dosing 50 mg/kg/day in three divided doses.</p>	Unknown; structurally similar to gamma aminobutyric acid (GABA); possible action via voltage-gated calcium channels.	<p>Patients aged 12 and older: Dizziness, ataxia, fatigue, nystagmus, somnolence.</p> <p>Patients aged 3–11: Fever, viral infection, nausea, vomiting, somnolence, hostility.</p>	Category C	<p>Neuropsychiatric adverse events especially in patients aged 3–11, suicidality, increased seizure frequency with abrupt discontinuation, SUDEP, tumorigenic potential, DRESS syndrome, multiorgan hypersensitivity.</p>	<p>Interactions with other AEDs: no significant</p> <p>Interactions with other medications: gabapentin taken concurrently with other pain medications leads to minor changes in levels of involved medications (see text for details).</p> <p>Gabapentin bioavailability decreased if coadministered within 2 hours of taking antacid.</p>

(continued)

**Table 27.1 Summary of Second-Generation AEDs (continued)**

<b>Topiramate</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Initial monotherapy or adjunctive therapy in partial onset and primary generalized seizures in patients aged 2 and older, adjunctive therapy in seizures associated with Lennox-Gastaut in patients aged 2 and older.	Monotherapy: 25mg BID x week 1 50 mg BID x week 2 75 mg BID x week 3 100 mg BID x week 4 150 mg BID x week 5 200 mg BID x week 6 Adjunctive therapy for partial onset: 25–50 mg/day, increase by 25–50 mg/day each week to goal dosing. Adjunctive therapy for primary generalized: 25–50 mg/day, increase by 25–50 mg/day each week to goal dosing.	Monotherapy: 400 mg/day in two divided doses Adjunctive therapy for partial onset: 200 mg/day to 400 mg/day in two divided doses Adjunctive therapy for primary generalized: 400 mg/day in two divided doses	Monotherapy initiation ages 2–10: 25 mg/day qhs x week 1, 50 mg/day qhs x week 2, increase dosage by 25–50 mg/day each subsequent week to goal dosing administered in two divided doses Monotherapy goal dosing ages 2–10: -Administered in two divided doses -Less than or equal to 11 kg: 150–250 mg/day -12–22 kg: 200–300 mg/day -23–31 kg: 200–350 mg/day -32–38 kg, 250–350 mg/day -greater than 38 kg: 250–400 mg/day. Monotherapy for children older than 10: same initiation and goal dosing as adults. Adjunctive therapy initiation dosing for partial onset, primary generalized, Lennox-Gastaut aged 2–16: -1–3 mg/kg/day qhs x week 1 -increase by 1–3 mg/kg/day every 1–2 weeks. -administer in two, equally divided doses starting in week 2 Adjunctive therapy goal dosing for partial onset, primary generalized, Lennox-Gastaut aged 2–16: total daily dose 5–9 mg/kg/day in two equally divided doses. Adjunctive therapy for children older than 16: same Initiation and goal dosing as adults.	Unknown; Possible actions include: blocking of voltage-dependent sodium channels, antagonizing glutamate receptor at the AMPA-kainate subtype of the receptor, augmenting activity of GABA at some subtypes of GABA-A receptor, inhibiting particular isozymes of the carbonic anhydrase enzyme.	Paresthesias, anorexia, weight loss, fatigue, dizziness, psychomotor slowing, cognitive problems, difficulty with concentration and memory, nervousness, confusion, mood problems, infection, fever, flushing.	Category D	Acute myopia, secondary angle closure glaucoma, oligoohidrosis and associated hyperthermia, metabolic acidosis, suicidality, cognitive side effects, neuropsychiatric side effects, fetal toxicity, increased seizure frequency with abrupt discontinuation, SUDEP, hyperammonemia with and without accompanying encephalopathy, nephrolithiasis, hypothermia with and without hyperammonemia with concomitant valproate use.	Interactions with other AEDs: topiramate levels significantly reduced by carbamazepine and phenytoin and slightly reduced by lamotrigine; coadministration with valproate has risk for hyperammonemia with and without accompanying encephalopathy and risk for hypothermia with and without hyperammonemia. Interactions with other medications: Possible decreased efficacy of oral contraceptive, increased lithium levels with high dose topiramate, exacerbation of metabolic acidosis with metformin and other carbonic anhydrase inhibitors.

(continued)



**Table 27.1 Summary of Second-Generation AEDs (continued)**

**Levetiracetam**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Partial onset seizures in patients one month of age and older with epilepsy. Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy. Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.	1,000 mg/day	1,000–3,000 mg/day	Start at 20 mg/kg/d and increase up to 60 mg/kg/day.	Not definitively known, but binds to the synaptic vesicle protein 2A thus interfering with neurotransmitter release and synaptic transmission.	Somnolence and fatigue, coordination difficulties, and behavioral abnormalities.	C	Monitor for suicidal ideation and worsening depression.	No known significant interactions known.

**Oxcarbazepine**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Monotherapy for partial seizures in patients 4–16 years. Adjunctive therapy for partial seizures in adults and children 2–16 years.	Initiated with a dose of 600 mg/day	Daily dose for adjunctive therapy is 1,200 mg/day. Whereas maximum dose for monotherapy with oxcarbazepine is 2,400 mg/day.	Initiated at a daily dose of 8–10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The maximum maintenance dose of Trileptal should be achieved over 2–4 weeks and should not exceed 60 mg/kg/day in a BID regimen.	The exact mechanism of action is unknown. Some in vitro electrophysiological studies indicate that they block voltage-sensitive sodium channels causing inhibition of repetitive neuronal firing, decreasing propagation of synaptic impulses and stabilizing hyper-excited neural membranes.	Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.	C	Hyponatremia. Stevens-Johnson syndrome (SJS), Angioedema.	Carbamazepine, phenytoin and phenobarbital all have been shown to decrease the plasma levels of MHD up to 29%-40% and verapamil by 20%. OCPs may be less effective with concurrent use of oxcarbazepine, lamotrigine and topiramate levels lower and phenytoin levels higher.

(continued)

**Table 27.1 Summary of Second-Generation AEDs (*continued*)**

<b>Tiagabine</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for partial seizures in patients aged 12 and older.	<p>Patients on hepatic enzyme-inducing medications:</p> <ul style="list-style-type: none"> <li>-Initiation dose 4 mg/day daily x week 1</li> <li>-8 mg/day in two divided doses x week 2</li> <li>-12 mg/day in three divided doses x week 3</li> <li>-16 mg/day in two to four divided doses x week 4</li> <li>-20–24 mg/day divided in two to four doses x week 5</li> <li>-24–32 mg/day in two to four divided doses x week 6.</li> </ul> <p>Patients not on hepatic enzyme-inducing medications: Lower doses, slower titration, no official dosing recommendations exist.</p>	<p>Patients on hepatic enzyme-inducing medications:</p> <p>24–32 mg/day in two to four divided doses.</p> <p>Maximum dosing in patients on hepatic enzyme-inducing medications:</p> <ul style="list-style-type: none"> <li>-12 to 18 year olds: 32 mg/day in two to four divided doses.</li> <li>-Over age 18: 56 mg/day in two to four divided doses.</li> </ul> <p>Patients not on hepatic enzyme-inducing medications: Lower doses, slower titration, no official dosing recommendations exist.</p>	Start at 4 mg per day & increase by 4 or 8 mg per week to a max dose of 32 mg/day.	Not fully understood; thought to enhance activity of gamma aminobutyric acid (GABA).	Depersonalization, dysarthria, euphoria, hallucination, hyperkinesia, hypertonia, hypesthesia, hypokinesia, hypotonia, migraine, myoclonus, paranoid reaction, personality disorder, hyporeflexia, stupor, twitching and vertigo. Hypertension, palpitation, syncope, and tachycardia.	Category C	<p>When used for other indications, tiagabine has been associated with new onset seizures and status epilepticus in patients without epilepsy.</p> <p>In nonepileptic patients who develop seizures while on tiagabine treatment, tiagabine should be discontinued and patients should be evaluated for an underlying seizure disorder.</p>	<p>Interactions with other AEDs: tiagabine clearance is increased by carbamazepine, phenytoin, phenobarbital, primidone; tiagabine levels not significantly affected when administered with valproate.</p> <p>Interactions with other medications: No significant interactions.</p>

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# Third-Generation Antiepileptic Drugs

Cesar C. Santos

## 28

### CHAPTER

The U.S. Food and Drug Administration (FDA) approved the third-generation antiepileptic drugs (AEDs) between 2004 and 2012. The AEDs included in this category include pregabalin, lacosamide, rufinamide, vigabatrin, clobazam, ezogabine, and perampanel. Though many of these are truly new compounds, some like vigabatrin and clobazam have been available outside the United States long before they were approved for use in the United States. This chapter focuses on these AEDs, and a summary of their various properties is presented in Table 28.1 (located at the end of the chapter).

#### PREGABALIN

##### Indications

Pregabalin is an AED used as an adjunct therapy for partial seizures with or without secondary generalization and in the management of patients with neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury, postherpetic neuralgia, and fibromyalgia. In 2007, pregabalin became the first medication that was FDA approved for the treatment of fibromyalgia. Although not FDA approved for this indication, it has been found effective in treating patients with generalized anxiety disorder.

##### Dosing

The available preparations of pregabalin include capsules of 25, 50, 75, 100, 200, 225, and 300 mg and an oral solution containing 20 mg/ml. Pregabalin is given orally with or without food. If it needs to be discontinued, gradual tapering over a minimum of 1 week is recommended. The usual starting dose is 150 mg/day (either 50 mg three times a day or 75 mg twice a day). Since pregabalin is primarily eliminated by renal excretion, dose adjustment is recommended based on renal function (Table 28.2).

A dose of 150 mg to 600 mg per day of pregabalin has been shown to be effective as adjunct treatment of partial seizures with or without secondary generalization in adults. Efficacy and adverse events are both dose related. The

recommended starting dose is 150 mg/day (either 75 mg given twice a day or 50 mg given three times a day). Based on response and tolerability, the dose can be adjusted to a maximum dose of 600 mg/day.

When used for neuropathic pain associated with diabetic peripheral neuropathy, the recommended maximum dose of pregabalin is 100 mg given three times a day in patients with creatinine clearance of at least 60 ml/min. For neuropathic pain associated with spinal cord injury, the recommended dose is 150 mg to 600 mg per day. In postherpetic neuralgia the recommended dose is 75 mg to 150 mg given twice a day or 50 mg to 100 mg given three times a day (150 mg to 300 mg/day) in patients with creatinine clearance of at least 60 ml/min. The recommended dose for fibromyalgia is 300 mg to 450 mg per day. A dose above 450 mg/day is not recommended.

##### Pharmacology

In the central nervous system, pregabalin binds to the  $\alpha 2$ -delta subunit of the voltage-dependent calcium channel. It decreases the release of several neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide, which may account for its ability to reduce neuronal excitability and seizures *in vivo*.

Peak plasma concentration of pregabalin occurs within an hour when taken on an empty stomach. When taken with food, pregabalin decreases  $C_{\max}$  by 25% to 30% and  $T_{\max}$  by 2.5 hours. However, food does not affect the extent of absorption. Pregabalin is not bound to plasma proteins. The volume of distribution is 0.56 l/kg. Half-life is 6.3 hours. Metabolism of pregabalin in humans is negligible. Major metabolite is *N*-methyl pregabalin. About 98% of pregabalin is excreted unchanged in the urine. Renal clearance is 73 ml/minute.

##### Efficacy Data

Three randomized, double-blind, placebo-controlled studies involving a total of 1,052 patients with refractory partial seizures, 12 years and older, showed significant

**TABLE 28.2 Pregabalin Dosage Adjustment Based on Renal Function**

CREATININE CLEARANCE (CRCL ML/MIN)	TOTAL PREGABALIN DAILY DOSE (MG/DAY)				DOSE REGIMEN
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

improvement in seizure control at 150, 300, and 600 mg/day with a clear dose–response relationship. Almost 50% of patients receiving 600 mg/day achieved greater than or equal to 50% seizure reduction. There was no difference between a twice-a-day (BID) and three times-a-day (TID) dosing schedule. Efficacy became evident as early as the first week of treatment (1).

### Efficacy in Other Conditions

In patients with neuropathic pain associated with diabetic peripheral neuropathy, a 6-week, double-blind, placebo-controlled trial involving 246 patients showed significant improvement in mean pain score (4.3 vs. 5.6 for placebo,  $P = .0002$ ) and an increase in the number of patients with greater than or equal to 50% decrease from baseline pain (39% vs. 15% for placebo,  $P = .002$ ) at 600 mg/day dose schedule (2).

A 12-week, multicenter, placebo-controlled trial was conducted in patients with neuropathic pain associated with spinal cord injury. A total of 137 patients were randomized to either placebo or flexible dose of pregabalin (150 to 600 mg/day) while continuing on their stable pain medication. The primary endpoint was the endpoint mean pain score (last 7 days daily pain diary entry). The endpoint mean pain score for the pregabalin-treated group was 4.62 compared with 6.27 for the placebo group ( $P < .001$ ). Treatment response was seen as early as week one and maintained throughout the stabilization phase. Pregabalin treatment was also associated with significant improvement in sleep (3).

In a postherpetic neuralgia trial, pregabalin-treated patients receiving either 600 mg/day (CrCl >60 ml/min) or 300 mg/day (CrCl 30–60 ml/min) showed significant improvement in endpoint mean pain scores (mean of the last seven daily pain ratings), 3.60 vs. 5.29 for placebo ( $P = .0001$ ). In addition, patients receiving pregabalin had significant improvement in sleep ( $P = .001$ ) (4).

Fibromyalgia treatment trials also showed improvement with pregabalin. Placebo was compared with 150, 300, and 450 mg/day dose of pregabalin in an 8-week trial looking at pain, sleep, fatigue, and health-related quality of life (QOL) in 529 patients with fibromyalgia syndrome. The 450 mg/day of pregabalin arm resulted in (a) significant improvement in pain severity, (b) significantly more patients with greater than or equal to 50% improvement in pain at the end point, and (c) significant improvement in sleep quality, fatigue, and several domains of health-related QOL (5).

### Adverse Effects

The most common side effects of pregabalin are dizziness, drowsiness, dry mouth, edema, blurred vision, weight gain, and difficulty concentrating. Other side effects include thrombocytopenia and increased creatinine kinase. Rarely, pregabalin has been associated with angioedema.

### Toxicity, Overdose, and Contraindications

Patients with severe renal failure on pregabalin may develop myoclonus as a result of gradual drug accumulation.

### Warnings and Precautions

As with all other AEDs, suicidal behavior and ideation are listed as possibly occurring with pregabalin. Patients should be monitored for signs and symptoms of depression or worsening depression, suicidal ideation or behavior, and/or unusual changes in mood or behavior.

### Teratogenicity

There are no adequate studies of pregabalin in pregnant women. Pregabalin is a Pregnancy Category C drug. Animal studies have shown increased incidence of fetal

structural abnormalities as well as other manifestation of developmental toxicity like lethality, growth retardation, and functional impairment of both nervous and reproductive systems.

Pregabalin is excreted in breast milk of rats. Although it is unknown whether this is true in humans, pregabalin use is not recommended while breastfeeding.

### Special Safety Concern

Drugs that depress the central nervous system (CND), including alcohol, may increase the sedative effects of pregabalin. Pregabalin can cause rhabdomyolysis, and, as noted earlier, rarely can cause angioedema.

### Drug Interactions

Owing to the pharmacokinetics of pregabalin, it is unlikely to be affected by other drugs through metabolic interactions or protein binding displacement. There are no reported pharmacologic interactions in vivo. However, it may have some potential interaction with opioids, benzodiazepines, barbiturates, ethanol, and other CNS depressant medications. It is a Schedule V drug, classified as a CNS depressant. Use of pregabalin with pioglitazone (Actos) and rosiglitazone (Avandia) may cause weight gain, fluid retention, and possibly heart failure.

### Use in Special Population

Since pregabalin is eliminated primarily by renal excretion, the dose needs to be adjusted in patients with reduced renal function. Dose adjustment is calculated based on creatinine clearance (Table 28.2). The use of pregabalin in preclinical trials in patients with diabetic neuropathy and epilepsy failed to show liver toxicity. However, postmarketing use has shown a rare instance of mild liver injury without jaundice with onset of symptoms within 3 to 14 days. Both cholestatic and hepatocellular patterns have been reported. The mechanism of injury is presumed to be idiosyncratic. The safety and efficacy profile of pregabalin is similar in the elderly and younger patients.

### Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

## LACOSAMIDE

### Indications

Lacosamide is indicated as an adjunct treatment of partial seizures in patients 17 years of age and older. Recently, it was also approved for use in monotherapy in patients with partial seizures aged 17 years and older.

### Dosing

Lacosamide is available as tablets of 50 mg, 100 mg, 150 mg, and 200 mg concentrations, injections of 10 mg/ml for intravenous infusion and oral solution of 10 mg/ml. It may be taken with or without food. For treatment of partial-onset seizures, lacosamide can be started via either an oral or intravenous administration. The initial recommended dose is 50 mg twice a day. The dose can be increased weekly by 100 mg up to the recommended maintenance dose of 200–400 mg/day based on response and tolerability.

When lacosamide needs to be switched from oral to IV dosing, the initial IV dose should be equivalent to the total daily dose and frequency of oral dosing. Each IV dose should be infused over a period of 30 to 60 minutes. When switching IV lacosamide to oral dosing, the oral dose should be equivalent to the total daily IV dose and administered twice daily.

### Pharmacology

The exact mechanism of action of lacosamide is unknown. In vitro studies have shown that it selectively enhances slow inactivation of voltage-gated sodium channels, which results in stabilization of hyperexcitable neuronal membranes and inhibition of neuronal firing. Previously it was also thought to bind to collapsing response mediator protein-2 (CRMP-2), a phosphoprotein mainly expressed in the nervous system and known to be involved in neuronal differentiation and control of axonal outgrowth. Recent data suggest that at therapeutic doses this may not occur.

Lacosamide is completely absorbed. Both the rate and extent of absorption are not affected by food. Bioavailability of orally administered lacosamide is about 100%. The elimination half-life is 13 hours and steady state is reached after 3 days of twice-a-day dosing. The peak plasma concentration is reached at the end of IV infusion and in 1 to 5 hours following oral administration. The volume of distribution is about 0.6 L/kg. Protein binding is less than 15%, and there is a linear relationship at a dose range of 100 to 800 mg/day. Elimination is primarily by renal excretion with 40% of the drug being excreted in the unchanged form. Metabolism of lacosamide is via the CYP2C19 system. Although peak concentrations are unchanged, in patients with mild–moderate renal impairment (creatinine clearance [CrCl] of 30–80 ml/min) and in patients with severe renal impairment (CrCl of 30 ml/min or less), the area under the curve (AUC) for lacosamide is increased by 25% and 60%, respectively. Dose adjustments are recommended. Dose adjustment is also recommended following hemodialysis because there can be as much as 50% reduction in the lacosamide AUC. Compared with healthy volunteers, the AUC of lacosamide is 50% to 60% higher in patients with moderate hepatic impairment. Dosage adjustment is also recommended in patients with mild–moderate hepatic impairment. Use of lacosamide in patients with severe hepatic impairment is not recommended.

### Efficacy Data

Efficacy data for lacosamide as adjunctive therapy for partial-onset seizures comes from three randomized, double-blind, placebo-controlled, multicenter studies. All studies involve adult patients with medically refractory partial seizures on one to three AEDs. Study designs were similar including the inclusion criteria and dose of lacosamide. A 50% reduction in seizure frequency was comparable among the three studies, 38% to 41%, at 400 mg and 600 mg/day dose given twice a day, which was statistically superior compared to placebo (6–8). In addition, an open-label extension study showed a 50% or greater reduction in seizures in 46.6% of patients. A conversion to monotherapy trial demonstrated that patients treated with lacosamide 300 mg and 400 mg/day dose exited the trial less often than historical controls (9).

### Efficacy in Other Conditions

Lacosamide has been studied in painful diabetic neuropathy, but is not currently approved for use in that indication.

### Adverse Effects

The most common adverse effects of lacosamide are diplopia, headache, dizziness, and nausea.

### Toxicity, Overdose, and Contraindications

There are no absolute contraindications noted for lacosamide.

### Warning and Precaution

As with all AEDs, suicidal behavior and ideation can occur with lacosamide. It can cause dizziness and ataxia. The utility of lacosamide should be seriously evaluated in patients with cardiac conduction problems like second-degree atrioventricular (AV) block, those who are taking drugs known to cause prolongation of the PR interval, and patients with severe cardiac disease. Lacosamide may also cause syncope. It should be withdrawn gradually in patients with epilepsy to minimize the potential of increased seizure frequency. Rare cases of multi-organ hypersensitivity reactions have been reported.

### Teratogenicity

There is no adequate data from the use of lacosamide in pregnant women. It should be used during pregnancy when its benefits clearly outweigh the unknown risks. There are also no data whether lacosamide is excreted in human breast milk. It is recommended that breastfeeding be discontinued during use of lacosamide.

### Special Safety Concern

Although peak concentrations are unchanged, in patients with mild–moderate renal impairment (CrCl of 30–80 ml/

min) and in patients with severe renal impairment (CrCl of 30 ml/min or less), the area under the curve (AUC) for lacosamide is increased by 25% and 60%, respectively. Dose adjustments are recommended. Dose adjustment is also recommended following hemodialysis because there can be as much as 50% reduction in the lacosamide AUC. Compared with healthy volunteers, the AUC of lacosamide is 50% to 60% higher in patients with moderate hepatic impairment. Dosage adjustment is also recommended even in patients with mild–moderate hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

### Drug Interaction

There is no known relevant drug–drug interaction between lacosamide and common AEDs.

### Use in Special Population

The use of lacosamide in patients with renal and hepatic impairment has been discussed earlier. In geriatric use, the AUC was 30% and 50% higher in men and in women, respectively, over the age of 75 years.

### Pediatric Use

Lacosamide is not approved for use in children under age 17 years.

## RUFINAMIDE

### Indication

Rufinamide is indicated as an adjunct treatment of drop attacks associated with Lennox-Gastaut syndrome (LGS).

### Dosing

Rufinamide is available for oral administration in 200 mg and 400 mg scored, film-coated tablets. It is also available in a liquid (40 mg/ml) formulation. In children 4 years and older with LGS, rufinamide should be started at a daily dose of 10 mg/kg/day given in two equally divided doses. The dose can be increased by 10 mg/kg every other day to a target dose of 45 mg/kg/day or 3,200 mg/day, whichever is less, administered in two equally divided doses. In adults with LGS, rufinamide should be started at a daily dose of 400–800 mg/day given in two equally divided doses. It can be increased by 400–800 mg every other day to a maximum dose of 3,200 mg/day, administered in two equally divided doses. Rufinamide should be given with food.

### Pharmacology

Rufinamide is a triazole derivative. The exact mechanism of action is unknown. In experimental models, it has been shown



to suppress hyperexcitability of neurons by prolonging the inactivation phase of the voltage-gated sodium channels. At relatively high concentrations, rufinamide has an inhibitory effect on mGluR5 receptor subtype.

The peak plasma concentration ( $T_{max}$ ) for rufinamide is reached between 4 and 6 hours with or without food. The rate of absorption and degree of exposure, however, can be maximized if rufinamide is taken with food. Plasma proteins do not extensively bind it. However, the absorption rate is very slow with peak plasma concentration occurring 4 to 6 hours after oral intake. It is estimated that greater than 85% of an orally administered 600 mg dose is absorbed in healthy volunteers. Absorption decreases with increasing dose.

The elimination half-life is between 6 and 10 hours. Steady state is reached within 2 days. Rufinamide pharmacokinetics is not affected by impaired renal function. However, patients on dialysis may experience up to 30% reduction in exposure so dose adjustment may have to be considered. Only about 34% of rufinamide is bound to plasma proteins, and so the potential for drug–drug interaction through displacement is very small. The volume of distribution is dose dependent.

Rufinamide is metabolized via hydrolysis by carboxylesterases to a pharmacologically inactive metabolite, carboxylic acid derivative, which is excreted in the urine. It is not metabolized by the cytochrome P450 but is considered a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4. Elimination half-life is between 6 and 10 hours. Rufinamide is primarily excreted via the kidneys.

### Efficacy Data

Rufinamide was tested in a randomized, double-blind, placebo-controlled study, which showed a median reduction in the frequency of total seizures (32.7% vs. 11.7%,  $P = .0015$ ) and tonic–atonic seizures (42.5% reduction vs. 1.4% increase,  $P < .0001$ ) in patients receiving drug compared with patients on placebo (10). A large Phase 2, double-blind, randomized, placebo-controlled study showed a significant, linear dose–response relationship ( $P = .003$ ) at doses of 200, 400, 800, and 1,600 mg/day (11). Rufinamide was also tested in adults with partial-onset seizures, but the drug does not have an indication for partial-onset seizures in adults.

### Efficacy in Other Conditions

Rufinamide has not been tested in detail in conditions other than epilepsy.

### Adverse Effects

The most commonly reported adverse reactions that occur with rufinamide include headaches, dizziness, fatigue, somnolence, and nausea

### Toxicity, Overdose, and Contraindications

Rufinamide is contraindicated in patients with familial short QT syndrome.

### Warning and Precaution

As with all other AEDs, rufinamide can cause suicidal behavior and ideation. It has been associated with multiorgan hypersensitivity reactions. Caution should be exercised when using rufinamide concomitantly with other drugs that shorten the QT interval. Rufinamide should be withdrawn slowly to minimize the risk of withdrawal seizures, seizure exacerbation, or status epilepticus.

### Teratogenicity

Rufinamide is a Pregnancy Category C AED. Studies in animals reveal no teratogenic effects. There are no clinical data on exposed pregnancies. However, rufinamide should not be taken during pregnancy and in women of childbearing age not using contraceptive measures unless clearly necessary. Although there are no data to suggest that rufinamide is excreted in breast milk, breastfeeding should be avoided during maternal use of rufinamide due to potential harmful effects.

### Special Safety Concerns

A relatively unique safety issue with rufinamide is that it has been shown to shorten the QT interval on electrocardiography (ECG). For this reason, it is contraindicated in patients with familial short QT syndrome. In addition, it should be used with caution in patients taking other medications with the same effect. As noted earlier, rufinamide can cause multiorgan hypersensitivity reactions like drug reactions with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome.

### Drug Interaction

Rufinamide has been shown to increase the serum phenytoin by as much as 21% with potential for further increases due to the dose-dependent pharmacokinetics of phenytoin. It also increases the clearance of carbamazepine and lamotrigine and decreases the clearance of phenobarbital. Valproic acid can increase the serum concentration of rufinamide by as much as 70% in children. It is recommended to decrease the dose of rufinamide to less than 400 mg in adults and by 50% to 60% in children when used concomitantly with valproic acid. It should be titrated upward slowly when starting rufinamide as an add-on AED to valproic acid. Rufinamide can decrease the effectiveness of oral contraceptives with ethinyl estradiol and norethindrone.

### Use in Special Population and Pediatric Use

The pharmacokinetics of rufinamide is similar in patients with severe ( $\text{CrCl} < 30 \text{ ml/min}$ ) renal impairment and that of healthy volunteers. However, dose adjustment is recommended when using rufinamide during dialysis. Although there are no specific studies addressing the effect of rufinamide in patients with hepatic impairment, its use is not recommended in patients with severe hepatic impairment. Rufinamide clinical studies did not include sufficient number of patients 65 years and older to determine if there are particular efficacy and safety considerations in this population.

#### Pediatric Use

Rufinamide is indicated as an adjunctive treatment in children with seizures secondary to LGS. Its use in children less than 4 years has not been established. In children over age 4 years, the pharmacokinetics of rufinamide is similar to that in adults.

### VIGABATRIN

#### Indication

Vigabatrin is indicated for the treatment of infantile spasms (IS) (in children aged 1 month–2 years of age) and as adjunctive treatment of refractory complex partial seizures in adults for whom the benefits outweigh the potential risk of vision loss.

#### Dosing

Vigabatrin is available in powder form for oral solution (500 mg) and in tablet form (500 mg). It should be given in two divided doses starting at an initial dose of 50 mg/kg/day. This can be titrated slowly (25–50 mg/kg/day) up to a maximum dose of 150 mg/kg/day.

#### Pharmacology

The exact mechanism of action of vigabatrin is unknown. It is presumed to exert its anticonvulsant property by irreversibly inhibiting gamma-aminobutyric acid transaminase (GABA-T) resulting in increased levels of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the CNS.

Vigabatrin has a linear pharmacokinetic pattern with a half-life of about 7.5 hours. Following oral administration, it is absorbed completely with a  $T_{\text{max}}$  of 1 hour following a single as well as multiple doses. When taken with food, the  $C_{\text{max}}$  is decreased by 33%,  $T_{\text{max}}$  is increased to 2 hours, and the AUC is unchanged. Vigabatrin does not bind to plasma proteins. The volume distribution for vigabatrin is 1.1 L/kg. It induces CYP2C9. Vigabatrin is not significantly metabolized and is primarily eliminated via the kidneys.

### Efficacy Data

Vigabatrin's efficacy data for the treatment of medically refractory complex partial seizures was derived from two separate randomized, double-blind, placebo-controlled studies. One study compared the efficacy and safety of vigabatrin up to 3 g/day dose with placebo in a double-blind, placebo-controlled fashion. A total of 182 patients were enrolled. This study showed that 3 g of vigabatrin was not only well tolerated, but it was significantly more effective than placebo as an add-on therapy for complex partial seizures (12). The second study was a dose-response study comparing 1 g, 3 g, or 6 g of vigabatrin to placebo. This study showed significant improvement in seizure control compared with placebo ( $\geq 50\%$  reduction in seizure frequency of 7% for placebo vs. 24%, 51%, and 54% for 1 g, 3 g, and 6 g doses, respectively). The 6 g/day dose was not significantly different compared with 3 g/day dose (13).

Two studies were used to evaluate vigabatrin's effectiveness in IS for FDA approval (14). The first study was a multicenter, randomized study comparing low-dose (18–36 mg/kg/day) and high-dose (100–148 mg/kg/day) vigabatrin in patients with both symptomatic and cryptogenic infantile spasms. Seventeen (16%) infants treated with high-dose vigabatrin became spasm free compared with only 7% in the low-dose group. Another study involved 40 patients. It was a multicenter, randomized, double-blind, placebo-controlled study in which infants were started on 50 mg/kg/day and based on response, titrated to 150 mg/kg/day. The end point was the percent change in spasm frequency. There was no difference in primary end point. However, a posthoc review showed a significant overall reduction in spasms in the treatment group (68.9% vs. 17% in the controls).

#### Efficacy in Other Conditions

Vigabatrin has not been tested in detail in conditions other than epilepsy.

#### Adverse Effects

The most commonly reported adverse effects include headache, somnolence, fatigue, dizziness, convulsion, nasopharyngitis, weight gain, upper respiratory infection, visual field defect, depression, tremor, nystagmus, nausea, diarrhea, memory impairment, insomnia, irritability, abnormal coordination, blurred vision, diplopia, vomiting, influenza, pyrexia, and rash.

#### Toxicity, Overdose, and Contraindications

Vigabatrin overdose has not resulted in death. However, it has caused coma, unconsciousness, and/or drowsiness. There is absolute contraindication to the use of vigabatrin.

## Warnings and Precautions

Vigabatrin can result in suicidal ideation and behavior, as can other AEDs. It should be withdrawn slowly to minimize the risk of withdrawal seizures, seizure exacerbation, or status epilepticus. Vigabatrin has been shown to cause peripheral neuropathy in adults. It can also cause weight gain and peripheral edema. Vigabatrin can cause visual changes, abnormal MRI findings, and neurotoxicity. These are discussed further.

## Teratogenicity

No significant data regarding the effects of vigabatrin on pregnancy are available. Vigabatrin is excreted in breast milk.

## Special Safety Concerns

Vigabatrin can cause permanent vision loss in infants, children, and adults. The extent of vision loss in infants and children is not well characterized. In adults, it causes concentric constriction of the visual field in over 30% of cases. In some cases, it can cause central retinal injury. The onset is unpredictable. It can occur within weeks of the start of treatment or at any time thereafter. Visual loss may worsen even after vigabatrin is discontinued. The risk increases with increasing dose and with cumulative exposure. Due to the significant nature of visual loss, vigabatrin should be discontinued within 2 to 4 weeks of treatment initiation if no substantial improvement in seizure control is appreciated. For those who are continued on treatment, periodic ophthalmologic evaluation starting at 4 weeks and every 3 months thereafter is recommended. Reassessment should also be done 3 to 6 months after vigabatrin is discontinued. It should not be used in patients with or who have increased risk of other irreversible visual impairment. Due to the significant risk of visual loss, vigabatrin is only available through a restricted distribution program called SHARE.

Vigabatrin causes MRI abnormalities characterized by symmetric increased T2 signal and restricted diffusion involving the thalamus, basal ganglia, brainstem, and cerebellum. This can be seen in up to 22% to 32% of patients, but it tends to resolve when vigabatrin is discontinued.

Neurotoxicity also occurs with vigabatrin. Vacuolization due to accumulation of fluid resulting in the separation of the outer layer of myelin has been reported in laboratory animals at doses within the therapeutic range used in humans. This lesion is referred to as intramyelinic edema (IME). Similar to the MRI abnormalities described earlier, these lesions tend to resolve when vigabatrin is discontinued.

## Drug Interaction

Vigabatrin can lower total plasma level of phenytoin by an average of 20%. This is due to induction of cytochrome

P450 2C. Similarly, phenobarbital level is reduced on average by 8% to 16% and valproic acid by 8%. Although these may not be clinically significant, dose adjustment may be warranted if clinically indicated. Conversely, concomitant use of carbamazepine, clorazepate, primidone, and sodium valproate do not affect the plasma concentration of vigabatrin.

## Use in Special Population

Dose adjustment of vigabatrin is recommended in patients with mild (CrCl 51–80 ml/min), moderate (CrCl 31–50 ml/min), and severe (CrCl 11–30 ml/min) renal impairment. The pharmacokinetics of vigabatrin has not been studied in patients with hepatic impairment. Although no studies involving sufficient number of patients aged 65 years and older, care should be taken when prescribing vigabatrin in this age group because of the potential coexisting impairment in renal function. Renal clearance of vigabatrin is 36% lower in healthy elderly subjects (>65 years) than in young healthy males. A single oral dose of 1.5 g of vigabatrin in elderly patients, greater than 65 years, with reduced creatinine clearance (<50 ml/min) can cause moderate to severe sedation and confusion, which can last up to 5 days.

## Pediatric Use

The safety or the efficacy of vigabatrin in children (<16 years of age) with complex partial seizures has not been established. Animal studies have shown both neurobehavioral (convulsions, neuromotor impairment, and learning deficits) and neuropathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals.

## CLOBAZAM

### Indication

Clobazam is a 1,5 benzodiazepine indicated as adjunctive therapy for seizures in Lennox-Gastaut syndrome (LGS) in patients 2 years and older.

### Dosing

Clobazam is available in 5 mg, 10 mg, and 20 mg tablets. It should be administered in two divided doses except the 5 mg dose, which can be given once a day. Although the dosing is based on body weight, it should be individualized based on efficacy and tolerability (Table 28.3). The steady state of clobazam and its active metabolite is attained in 5 and 9 days, respectively, so the dose should be increased no faster than weekly. Clobazam can be taken with or without food. The tablets can be taken whole or crushed and mixed with applesauce.

**Table 28.3 Recommended Total Daily Dosing Schedule for Clobazam**

	<30 KG BODY WEIGHT	>30 KG BODY WEIGHT
Starting dose	5 mg	10 mg
Starting day 7	10 mg	20 mg
Starting day 14	20 mg	40 mg

### Pharmacology

The exact mechanism of action of clobazam is unknown. Clobazam and its active metabolite, *N*-desmethyclobazam (norclobazam), work by potentiating GABAergic neurotransmission through its binding at the benzodiazepine site of the GABA<sub>A</sub> receptor.

Clobazam is rapidly and extensively absorbed with bioavailability of about 100%. The  $T_{max}$  is reached in 0.5 to 4 hours. Taking it with food or crushing the tablet and mixing it with applesauce do not affect absorption. The volume of distribution is 100 L. Protein binding is 80% to 90% for clobazam and 70% for *N*-desmethyclobazam. Clobazam has two major metabolites, *N*-desmethyclobazam and 4'-hydroxyclobazam. *N*-desmethyclobazam is active. Clobazam is extensively metabolized in the liver by *N*-demethylation primarily by CYP3A4, and to a lesser degree by CYP2C19 and CYP2B6. *N*-desmethyclobazam, on the contrary, is primarily metabolized by CYP2C19. Elimination half-life is 36 to 42 hours for clobazam and 71 to 82 hours for *N*-desmethyclobazam. About 82% is excreted in the urine.

### Efficacy Data

Efficacy data for clobazam are based on a trial of 217 patients with the primary end point of percentage reduction in the weekly drop seizures (atonic, tonic, or myoclonic) from the 4-week baseline period to the 12-week maintenance period (15). The study showed significant reduction in the average weekly drop seizures, 12.1% for placebo compared with 42.1%, 49.4% and 68.3% for 0.25, 0.5, and 1 mg/kg/day groups, respectively. The responder rates ( $\geq 50\%$  reduction of seizures) were 43.4%, 58.6%, and 77.6% for the same dose schedules compared with 31.6% for placebo.

### Efficacy in Other Conditions

Clobazam has not been tested in detail in conditions other than epilepsy.

### Adverse Effects

The most common adverse effects include somnolence or sedation, drooling, constipation, cough, urinary tract infection, fever, aggression, insomnia, dysarthria, and fatigue.

### Toxicity, Overdose, and Contraindications

Overdose can cause drowsiness, lethargy, ataxia, confusion, CNS depression, respiratory depression, coma, and death. There are no absolute contraindications to the use of clobazam.

### Warning and Precaution

As with other AEDs, it can result in suicidal behavior and ideation. Clobazam should be withdrawn slowly to minimize the risk of withdrawal seizures, seizure exacerbation, or status epilepticus. Withdrawal symptoms (psychosis, hallucinations, behavioral problems, tremor, and anxiety) may occur when clobazam is withdrawn abruptly. Somnolence and sedation can occur, which can be potentiated with concomitant use of other CNS depressants.

### Teratogenicity

Clobazam is a Category C AED. Neonatal withdrawal symptoms, hypothermia, hypotonia, respiratory difficulty, and feeding problems have been reported in infants born to mothers taking clobazam. Clobazam is excreted in breast milk, so its use in lactating women must be with care.

### Special Safety Concerns

Clobazam can be abused and it can cause dependence. It is a federally controlled substance (Class C-IV).

### Drug Interaction

Concomitant use of CNS depressants like alcohol, opioids or tricyclic antidepressants can exacerbate CNS depression. Alcohol increases maximum plasma concentration by 50%.

CYP2C19 inhibitors like fluconazole, fluvoxamine, ticlopidine, or omeprazole can increase *N*-desmethyclobazam, so dosage adjustment may have to be done. Hormonal contraceptives and other CYP3A4 substrates like midazolam may be affected. Clobazam may decrease the efficacy of oral contraceptives. Use of other forms of contraception is recommended. Strong CYP3A4 inhibitors like ketoconazole can increase clobazam's AUC by 54%.

### Use in Special Population

In patients with mild and moderate renal impairment, no dose adjustment of clobazam is needed. There are no available data for patients with severe renal impairment or end stage renal disease. The effect of hepatic impairment on the pharmacokinetics of clobazam is very limited although it is metabolized by the liver. At any given dose, the plasma concentration of clobazam is higher in the elderly. The starting dose should be 5 mg/day. The dose should be increased more slowly.



### Pediatric Use

The safety and efficacy of clobazam has not been established in patients less than 2 years of age.

## EZO GABINE

### Indication

Ezogabine, previously also known as retigabine, is FDA approved for use as an adjunctive therapy in patients with partial-onset seizures aged 18 years and older.

### Dosing

Ezogabine is available in tablets of 50 mg, 200 mg, 300 mg and 400 mg. The starting dose is typically 300 mg/day given on a TID schedule. The dose can be increased weekly by 150 mg/day (50 mg TID) up to a maximum of 1,200 mg/day. In clinical trials effective doses were found to be between 600–1,200 mg/day.

### Pharmacology

Ezogabine is the first AED thought to exert its antiepileptic effects by enhancing the activity of potassium channels. It activates KCNQ (Kv7) channels that results in an outward flow of potassium ions when activated. When neurons are depolarized, activation of the KCNQ (Kv7) channels opposes the depolarization with a potassium current efflux. This reduces the likelihood that sufficient depolarization will be reached to cause an action potential (16). There are also some data suggesting that ezogabine enhances GABAergic inhibition as well.

After oral administration, ezogabine is rapidly absorbed with a  $T_{max}$  of 0.5 hours. The half life is 6 to 10 hours, necessitating the TID dosing schedule. It has linear pharmacokinetics and a bioavailability of about 60% after oral administration. Absorption is not affected by food, but the  $T_{max}$  is delayed slightly. Ezogabine is metabolized by hydrolysis/acetylation and glucuronidation to its main metabolite, N-acetyl metabolite of ezogabine (retigabine) (NAMR). NAMR has inconsistent antiepileptic properties. Ezogabine and NAMR are 80% and 45% plasma protein bound, respectively. Both ezogabine and NAMR are eliminated primarily by the kidneys.

### Efficacy Data

Efficacy of ezogabine was established with one phase II and two phase III studies (17). Doses of 600 mg/day, 900 mg/day, and 1,200 mg/day (given on a TID schedule) were tested against placebo. In all studies, all three doses of ezogabine resulted in a statistically higher reduction of seizure frequency compared to placebo. The seizure reduction rates for 600 mg, 900 mg, and 1,200 mg doses were 23.4% to 28%, 29.3% to 40%, and 44%, respectively, compared to placebo

response of 13.1% to 18%. Long-term continuation studies demonstrated continued efficacy.

### Efficacy in Other Conditions

Ezogabine has been studied in a randomized control trial for the treatment of postherpetic neuralgia. Pain scores were not significantly different between drug and placebo.

### Adverse Effects

The most common adverse effects reported with ezogabine use are dizziness, somnolence, confusional state, tremor, impaired coordination, memory impairment, speech disorder, and blurred vision. These adverse effects were dose dependent. Bladder dysfunction, dysuria, urinary hesitation, skin discoloration, and visual disturbances have been reported as well and are discussed in more detail in the following.

### Toxicity, Overdose, and Contraindications

Very few instances of overdose have been reported with ezogabine. Overdose symptoms included agitation, aggressive behavior, and irritability. Asystole and ventricular arrhythmia occurred in two volunteers in an abuse potential study (16).

### Warning and Precaution

Ezogabine can cause retinal abnormalities and changes in visual acuity. Skin discoloration has been reported. Urinary retention can occur as well. These are discussed in more detail later. QT prolongation can occur on the ECG, and this should be especially monitored in patients on other concomitant medications that can also prolong the QT interval. Hallucinations and psychotic behavior can occur as well. Suicidal behavior and ideation can occur as with any AED.

### Teratogenicity

The true teratogenic potential of ezogabine is not known. It has a Pregnancy Category C rating. In animal models, it has been shown to cause developmental toxicity. Little human data are available. Use in pregnancy should only be undertaken when the benefits clearly justify the risks. It is not known whether ezogabine is secreted in human breast milk.

### Special Safety Concerns

There are several safety concerns with ezogabine that have resulted in limited clinical use of this AED. The most concerning is the potential for retinal changes. It can cause changes similar to those seen in retinal pigment dystrophies. Up to one-third of patients who used ezogabine for long term had such retinal changes. These changes may cause a reduction

in visual acuity, but their exact clinical significance is not entirely known. It is also not known whether these changes reverse with the discontinuation of the drug. Patients treated with ezogabine should undergo a baseline ophthalmologic examination, which should be repeated every 6 months. In addition, if clear benefit is not realized, discontinuation of the drug should be seriously considered.

A bluish discoloration of the skin has also been reported with ezogabine use. It is most commonly seen around the lips and nail beds. Discoloration of the palate and sclera has also been reported. This discoloration occurs in about 10% of patients treated with ezogabine. The clinical consequences, time to onset, pathophysiology, and reversibility of this is unknown.

Urinary retention was reported in up to 2% of patients enrolled in the ezogabine clinical trials. Patients often reported urinary hesitancy, urinary retention, or dysuria. Though some patients required urinary catheterization, these adverse effects were generally reversible with drug discontinuation. Ezogabine should be used with caution in patients with other reasons for urinary difficulty, such as patient with benign prostate hypertrophy. All patients should be monitored closely for urinary side effects.

### Drug Interaction

Enzyme-inducing AEDs like carbamazepine and phenytoin can reduce ezogabine plasma concentration, and consideration should be given to increasing the dose of ezogabine. Other, non-enzyme-inducing AEDs do not have a significant effect on ezogabine. Ezogabine causes reduction in lamotrigine plasma concentration, but this reduction is not considered clinically significant. Ezogabine and NAMR may increase digoxin serum concentration. Oral contraceptives containing norgestrel/ethinyl estradiol are not affected by ezogabine.

### Use in Special Population

In patients with mild ( $\text{CrCL} \geq 50$  to  $< 80$  mL/min) renal impairment, the AUC of ezogabine and NAMR was increased 30%. The AUC doubled in patients with moderate ( $\text{CrCL} \geq 30$  to  $< 50$  mL/min) renal impairment. When used in patients with renal impairment, the dose of ezogabine should be proportionately reduced. The effects of hemodialysis are not certain. Mild hepatic impairment did not affect ezogabine AUC, but moderate impairment resulted in the AUC being 30% higher. As with renal impairment, the dose of ezogabine should be reduced in patients with hepatic impairment. The AUC of ezogabine was almost 50% higher in elderly ( $> 65$  years) subjects compared to young adults. A lower dose should be used in the elderly.

### Pediatric Use

Ezogabine efficacy and pharmacokinetics have not been investigated in detail in children.

## PERAMPANEL

### Indication

Perampanel is indicated as an adjunct treatment of partial seizures with or without secondary generalization in patients with epilepsy aged 12 years and older.

### Dosing

In the absence of enzyme-inducing AEDs, perampanel may be initiated at 2 mg per day (usually at night). The dose can be increased by 2 mg/day increments at weekly intervals to 4 to 8 mg/day. In the presence of enzyme-inducing AEDs (phenobarbital, primidone, phenytoin, carbamazepine, oxcarbazepine, topiramate), it may be started at 4 mg per day and increased by 2 mg/day at weekly intervals to 8–12 mg/day.

### Pharmacology

Perampanel is a selective, noncompetitive  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist on postsynaptic neurons.

Perampanel is rapidly and completely absorbed following oral administration. Food does not affect the extent of absorption, but the rate of absorption is reduced.  $C_{\text{max}}$  is decreased by 28% to 40% and  $T_{\text{max}}$  is delayed by 2 to 3 hours. Perampanel is 95% protein bound. It has a long half-life, about 105 hours. Perampanel is primarily metabolized by CYP3A4, and it neither induces nor inhibits P450 enzymes. About 70% of the dose is excreted in the stool and about 30% in the urine.

### Efficacy Data

Efficacy data for perampanel come from three Phase III trials (18–20). One of these studies evaluated the safety and efficacy of 2, 4, and 8 mg/day perampanel added to one to three concomitantly used AEDs, while the other two used once-daily 8 or 12 mg perampanel dose. All three were multinational, multicenter, randomized, double-blind, placebo-controlled phase III trials. Addition of perampanel improved seizure control. The minimum effective dose was 4 mg/day and that 8 mg and 12 mg/day doses were safe, and the tolerability was acceptable.

### Efficacy in Other Conditions

Perampanel has not been tested in detail in conditions other than epilepsy.

### Adverse Effects

Common side effects include dizziness, drowsiness, fatigue, irritability, headache, falls, ataxia, upper respiratory tract infection, weight gain, vertigo, gait disturbance/balance

disorder, anxiety, blurred vision, dysarthria, weakness, aggression, and hypersomnia.

### **Toxicity, Overdose, and Contraindications**

There are no absolute contraindications; however perampanel should be used with caution in patients with aggression and agitation.

### **Warning and Precaution**

Perampanel is a schedule III controlled substance due to its potential for addiction. Serious neuropsychiatric side effects can occur. Suicidal behavior and ideation can occur as with any AED. In general, AEDs should be withdrawn slowly to minimize the risk of withdrawal seizures, seizure exacerbation, or status epilepticus. However, perampanel has a very long half life, which makes this less likely.

### **Teratogenicity**

Perampanel is a Pregnancy Category C drug. Administration throughout organogenesis in pregnant rats resulted in an increase in visceral abnormalities. It is not known whether perampanel is secreted in human breast milk.

### **Special Safety Concerns**

Perampanel can cause serious neuropsychiatric events like changes in mood or behavior (aggression, hostility, irritability, and anger), violent thoughts or threatening behavior, including homicidal ideation. These may occur in patients without prior neuropsychiatric history. Patients should be monitored closely for these side effects during the titration and at higher doses. This is, however, a rare side effect.

### **Drug Interaction**

Concomitant administration of enzyme-inducing AEDs may lower the plasma concentration of perampanel.

### **Use in Special Population**

In patients with mild-to-moderate renal impairment, perampanel dose should be titrated slowly and close monitoring is recommended. It is not recommended for patients with severe renal impairment or patients on hemodialysis. For patients with mild-to-moderate hepatic impairment, the initial dose is 2 mg per day. The dose may be increased by 2 mg/day at 2-week intervals to a maximum dose of 6 mg/day and 4 mg/day for patients with mild and moderate hepatic impairments, respectively. In geriatric patients, the same dose schedule should be followed.

### **Pediatric Use**

Safety and efficacy have not been established in patients younger than 12 years.

The third-generation AEDs offer drugs with unique mechanisms of action that further increase the treatment options available for the patient. Many of these drugs bring unique benefits, such as intravenous formulations, and unique challenges, such as ophthalmologic adverse effects. A better understanding of the features of these medications will enhance the providers' ability to prescribe the most appropriate AED.

TABLE 28.1 Summary of Third-Generation AEDs

<b>Pregabalin</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for partial -onset seizures in adults	150 mg/day	150–600 mg/day	N/A	Binds to alpha2-delta subunit of calcium channels	Dizziness, drowsiness, dry mouth, edema, blurred vision, weight gain, difficulty concentrating	C	Excessive sedation when mixed with other CNS depressants, angioedema, rhabdomyolysis	With other CNS depressants causes sedation
<b>Lacosamide</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Monotherapy and adjunctive therapy for partial onset seizures in adults	100 mg/day	200–400 mg/day	N/A	Enhances slow inactivation of voltage-gated sodium channels	Diplopia, headache, dizziness, nausea	C	Use with caution in patients with second-degree AV heart block, multi-organ hypersensitivity reactions	No clinically significant interactions
<b>Rufinamide</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for seizures in Lennox-Gastaut syndrome	10 mg/kg/day (children); 400–800 mg/day (adults)	45 mg/kg/day (children); 3,200 mg/day (adults)	45 mg/kg/day	Prolongs inactivation phase of voltage-gated sodium channels	Headache, dizziness, fatigue, somnolence, nausea	C	Shortens QT interval, multiorgan hypersensitivity reactions	Increases phenytoin and phenobarbital, decreases carbamazepine, lamotrigine; valproic acid can increase rufinamide levels; decreases effectiveness of oral contraceptives
<b>Vigabatrin</b>								
Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Infantile spasms; adjunctive therapy for partial onset seizures in children (10 years and older) and adults	50 mg/day (children); 1,000 mg/day (adults)	150 mg/kg/day (children); 3,000 mg/day (adults)	150 mg/kg/day	Inhibits GABA transaminase	Headache, somnolence, fatigue, dizziness, convulsions	C	Permanent vision loss, MRI white matter changes, myelin vacuolization	Decreases phenytoin, phenobarbital, valproic acid

(continued)



TABLE 28.1 Summary of Third-Generation AEDs (*continued*)**Clobazam**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for seizures in Lennox-Gastaut syndrome	5 mg/day (weight <30 kg); 10 mg/day (weight ≥30 kg)	20 mg/day (weight <30 kg); 40 mg/day (weight ≥30 kg)	20 mg/day	Potentiates GABAergic neurotransmission, binds at GABA <sub>A</sub> receptors	Somnolence, drooling, constipation, aggressive behavior	C	Can be abused; withdrawal symptoms include psychosis, hallucinations, anxiety; excessive sedation when combined with other CNS depressants	With other CNS depressants causes sedation; decreases effectiveness of oral contraceptives

**Ezogabine**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive treatment of partial onset seizures adults	300 mg/day	600–1,200 mg/day	N/A	Activation of voltage-gated potassium channels	Dizziness, somnolence, fatigue, confusional state	C	Vision changes, skin discoloration, urinary retention, QT prolongation	Decreases lamotrigine, increases digoxin, enzyme-inducing AEDs decrease ezogabine

**Perampanel**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive treatment of partial-onset seizures in children (12 years and older) and adults	2 mg/day (without enzyme inducing AEDs); 4 mg/day (with enzyme-inducing AEDs)	4–8 mg/day (without enzyme inducing AEDs); 8–12 mg/day (with enzyme-inducing AEDs)	4–8 mg/day	Selective, noncompetitive AMPA receptor antagonist	Dizziness, drowsiness, fatigue, irritability, headache	C	Aggressive behavior, homicidal ideation, anger, irritability	Enzyme inducing AEDs can decrease perampanel

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# Newest Antiepileptic Drugs and Drugs in Development

*K. Nicole Mims and Aatif M. Husain*

29

C H A P T E R

Despite the approval of many new antiepileptic drugs (AEDs) in the past 20 years, there are a sizable number of patients with epilepsy whose seizures remain refractory to medical therapy. There are a number of AEDs that are in various stages of development, and there is hope that these medications will provide more effective therapy with fewer adverse effects. The list of medications that are in development is constantly changing as some receive approval by regulatory agencies, while others are deemed not to be effective or provide a substantial improvement over currently available therapies. In this chapter, a few of these AEDs will be discussed. One of the medications discussed, eslicarbazepine, has recently received approval by the U.S. Food and Drug Administration (FDA). Brivaracetam and ganaxolone are in different stages of drug development. A summary of these agents is presented in Table 29.1 (located at the end of the chapter). There are several others as well, and the interested reader is referred to excellent resources that discuss these agents (1,2).

## ESLICARBAZEPINE

### Indications

Eslicarbazepine was recently approved by the FDA as adjunctive treatment of partial-onset seizures. Though not specifically stated, it is currently approved for use in adults. Pediatric safety data are not yet available.

### Dosing

Eslicarbazepine dosing should start at 400 mg/day. The dose can be increased by 400 mg every week to a maximum of 1,200 mg/day. The recommended daily dose is 800 mg, but it is recognized that some patients may need the higher dose. Side effects are more common at the higher dose. An investigation of twice-daily dosing of eslicarbazepine revealed a 33% lower concentration of eslicarbazepine when dosed twice daily as compared to once daily (3).

### Pharmacology

The exact mechanism of antiepileptic effect of eslicarbazepine is not known. However, it is thought that eslicarbazepine acts as a voltage-gated sodium channel blocker, which uniquely targets inactive sodium channels that have recently been open. This mechanism of action is theorized to allow eslicarbazepine to specifically target rapidly firing neurons.

Eslicarbazepine is available commercially as eslicarbazepine acetate. After absorption, eslicarbazepine acetate is virtually undetectable and is rapidly converted to eslicarbazepine. Eslicarbazepine exerts the antiepileptic effect. The  $C_{max}$  is achieved 1 to 4 hours post dose. The half-life is 13 to 20 hours and steady state is achieved in 4 to 5 days. Food does not affect absorption. Protein binding of eslicarbazepine is low, and thus does not affect many other drugs that are highly plasma protein bound. Eslicarbazepine is metabolized with first-pass metabolic hydrolysis primarily to S-licarbazepine. Approximately 5% of eslicarbazepine is metabolized to oxcarbazepine and R-licarbazepine. Contrary to its parent drugs, carbamazepine and oxcarbazepine, eslicarbazepine is not metabolized by the CYP system in the liver and is neither an inducer nor inhibitor of liver enzymes. Approximately one third of the metabolites undergo glucuronidation and the remainder is excreted unchanged. Elimination occurs via the kidneys.

### Efficacy Data

Four multicenter, double-blind, randomized, placebo-controlled trials were conducted to evaluate efficacy and safety of eslicarbazepine for treatment of adjunctive therapy in patients with refractory partial-onset epilepsy (3–6). Of these four trials, one trial focused on once-daily versus twice-daily dosing, finding decreased plasma concentration of eslicarbazepine in the twice-daily dosing group as mentioned earlier (3). The other three trials shared similar methodology with a baseline period during which seizure frequency was monitored, a brief titration period usually lasting a few

weeks and then a 14- to 18-week treatment period. All evaluated 800 mg and 1,200 mg/day dosing with two studies including 400 mg/day and one including 200 mg/day. All trials demonstrated decreased seizure frequency in the 800 mg and 1,200 mg/day treatment groups (35% and 39%, respectively) compared to placebo (15%), and there was no significant difference between the two doses (7).

### Efficacy in Other Conditions

Eslicarbazepine is FDA approved for only partial-onset seizures. However, studies are underway for its use treating in bipolar disorder and various pain syndromes. The pain syndromes that are being studied include fibromyalgia, postherpetic neuralgia, and painful diabetic neuropathy. Details of efficacy in these disorders are not yet available.

### Adverse Effects

The most common adverse events seen with eslicarbazepine are central nervous system (CNS) related and similar to those of other AEDs. The most common side effects are dizziness, somnolence, headache, and nausea. A relatively common unique side effect of eslicarbazepine is diplopia. Psychiatric side effects that may be seen include depression, agitation, and apathy. Rash has been reported as well, but when seen in clinical trials, it resolved with discontinuation of the medication. Hyponatremia has been reported as well, but the incidence is much lower than observed with carbamazepine or oxcarbazepine. It should be noted, however, that in the clinical trials, withdrawals occurred in up to 19% and 27% of the 800 mg and 1,200 mg/day groups compared to up to 7% with the placebo group (8).

### Toxicity, Overdose, and Contraindications

Acute toxicology studies revealed the estimated lethal dose of eslicarbazepine in the mouse and rat was 500 mg/kg when administered orally and 100 mg/kg when administered intravenously. Human toxicity levels are not known. The treatment of overdose is supportive. Gastric lavage and the use of activated charcoal should be considered. Eslicarbazepine is contraindicated in patients who have had an allergic reaction to oxcarbazepine.

### Warning and Precautions

Eslicarbazepine should be used with caution in patients with 2nd or 3rd degree atrioventricular (AV) heart block. This caution results from an increase in the PR interval on electrocardiograms (ECG) seen especially in patients taking 1,200 mg/day.

### Teratogenicity

Eslicarbazepine is a Pregnancy Category C AED. There are no adequately controlled human teratogenicity studies. Use of

this AED in pregnancy should clearly outweigh the potential known risk. Eslicarbazepine is excreted in breast milk, and caution is advised when used in women who are breastfeeding.

### Special Safety Concerns

As with all other AEDs, suicidal behavior and ideation is a concern. However, this is no more a concern than with other AEDs. Serious skin rashes have been reported, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In addition, multiorgan hypersensitivity, anaphylactic reactions, and angioedema have also been reported. Clinically significant hyponatremia (sodium <125 mEq/L) has been reported, but as noted earlier, it appears to be less common than with carbamazepine and oxcarbazepine.

### Drug Interactions

Eslicarbazepine interacts with various AEDs. When combined with phenytoin and phenobarbital, eslicarbazepine serum concentration is reduced. Although eslicarbazepine failed to demonstrate any interaction with carbamazepine or oxcarbazepine, this combination resulted in significantly increased incidence of diplopia, abnormal coordination, and dizziness.

Eslicarbazepine significantly increases the elimination rate of both hormonal components in oral contraceptives and can result in contraceptive failure. Although no effect is seen on anticoagulation, eslicarbazepine can result in decreased exposure of warfarin (8). Anticoagulation status should be carefully monitored in these patients.

### Use in Special Populations

Eslicarbazepine should be avoided in pregnancy and nursing mothers since its effects have not been assessed in these populations. In patients with renal impairment, clearance is decreased and total exposure increased. Reducing the eslicarbazepine dose is recommended in patients with severe renal impairment, but dose adjustment in mild or moderate renal impairment has not yet been elucidated. Dose adjustments are not necessary for mild or moderate hepatic impairment, but eslicarbazepine should not be used in patients with severe hepatic impairment.

### Pediatric Use

Eslicarbazepine has not been tested in pediatrics and use in this population is not currently recommended.

## BRIVARACETAM

### Indications

Brivaracetam is not currently approved by the FDA. Clinical trials have been performed in adults and children as adjunctive therapy for partial-onset and generalized seizures.



## Dosing

The dosing of brivaracetam has been investigated in several clinical trials in adults. Earlier studies investigated lower doses ranging from 10 mg/day to 80 mg/day. In these studies, higher doses of 50 mg/day and 80 mg/day were more effective than lower doses and placebo (9–11). Subsequent studies investigated higher doses up to 200 mg/day (2,12,13). Higher doses appeared to be more effective. The final recommended dose has not yet been determined.

## Pharmacology

Brivaracetam is a drug derivative of levetiracetam and as such shares levetiracetam's mechanism of action on synaptic vesicle protein 2A (SV2A). Brivaracetam's affinity for SV2A is estimated to be 25 times greater than that of levetiracetam. How binding to SV2A exerts antiepileptic effects is not known. It is thought that SV2A is involved with presynaptic exocytosis of intraneuronal vesicles. Drugs that bind to SV2A may disrupt this process and reduce excitatory neurotransmission. In addition, brivaracetam also inhibits neuronal voltage-dependent sodium channels (14).

Brivaracetam exhibits linear pharmacokinetics and is rapidly absorbed after oral administration. It is not highly protein bound (less than 20%) and has an average half-life of 7 to 8 hours, necessitating at least twice-daily dosing. It is extensively metabolized by hydrolysis via the cytochrome P450 system. The metabolites are inactive. Over 95% of the brivaracetam metabolites are excreted in urine (11).

## Efficacy Data

Several clinical trials documented the efficacy of brivaracetam in adults. Two Phase IIb and three Phase III trials have been completed assessing efficacy of brivaracetam as adjunctive therapy in patients with refractory partial-onset epilepsy or generalized epilepsies in adults (9–13). In one of the Phase IIb studies, doses of 5 mg/day, 20 mg/day, and 50 mg/day were compared to placebo. Only the 50 mg/day dose resulted in statistically significant reduction of seizure frequency compared to placebo (10). The other Phase IIb study evaluated 50 mg/day and 150 mg/day of brivaracetam compared to placebo. Neither dose resulted in statistically significant reduction in seizure frequency as compared to placebo (11).

Results from two of the Phase III studies have been published. In one study, 5 mg/day, 20 mg/day, and 50 mg/day doses were compared to placebo. Much like the Phase IIb study, in this study only the 50 mg/day dose resulted in a significantly lower (22%) seizure frequency/28 days compared to placebo (9). In the other Phase III study, higher doses of 50 mg/day and 100 mg/day were compared to placebo. Interestingly, the primary end point (percent reduction in seizures) was statistically significant for the 50 mg/day dose compared to placebo but not the 100 mg/day dose (13).

Another Phase III study that has recently been completed evaluated up to 200 mg/day. The final recommended dose has not been established yet.

## Efficacy in Other Conditions

Along with being investigated in various types of epilepsy, brivaracetam has been evaluated in postherpetic neuralgia. The results of these investigations are not yet known. The value of this medication in non-epilepsy-related conditions remains uncertain.

## Adverse Effects

The most common adverse effects reported with brivaracetam are headache, somnolence, dizziness, and fatigue. Other side effects include nasopharyngitis and urinary tract infection. Serious adverse events necessitating discontinuation of medication in clinical trials were aggression, anxiety, irritability, insomnia, depression, convulsions, and dizziness (2).

## Toxicity, Overdose, and Contraindications

Little information is available about brivaracetam toxicity. Transient, dose-related CNS effects were seen in toxicology studies in rats and mice, and these generally occurred above 100 mg/kg. Significant cardiac, respiratory, or gastrointestinal damage was not seen. Chronic use of high doses resulted in liver and biliary injury. In healthy volunteers, a study prescribing 1,000 mg/day or 800 mg twice daily failed to reveal any significant toxic effects and the adverse events noted were mostly CNS related. Vital signs, physical and chemical laboratory examinations remained normal. No clear contraindications exist at this time (2,14).

## Warning and Precautions

No clear warnings or precautions exist currently for brivaracetam. In general, it is a well-tolerated drug even at high doses and side effects are typically only mild to moderate, transient, and CNS related. All AEDs can cause suicidal ideation or behavior, and patients taking AEDs should be monitored for this. In a well-controlled QT safety study, cardiac repolarization was not affected.

## Teratogenicity

Teratogenicity data are not currently available as pregnant women and women who are nursing are excluded from participating in any of the clinical studies. During animal toxicity studies, brivaracetam doses up to 120 mg/kg/day were administered to rats and rabbits and failed to demonstrate any effect on fertility, pregnancy, or early embryonic development (15).

### Special Safety Concerns

Serological or other special monitoring is not necessary for brivaracetam. Toxicity studies revealed no alteration in chemistry laboratory data despite high doses of brivaracetam. Carbamazepine's 10,11 epoxide metabolite increases with addition of high-dose brivaracetam to carbamazepine, and if that occurs, carbamazepine levels as well as carbamazepine-induced side effects should be monitored.

### Drug Interactions

Brivaracetam demonstrates few drug–drug interactions with other AEDs. At brivaracetam doses of greater than 50 mg/day, the 10, 11 active epoxide metabolite of carbamazepine increased, and at a dose of 100–150 mg/day, the carbamazepine epoxide metabolite approached the upper limit of normal. Enzyme-inducing AEDs resulted in a slightly increased brivaracetam clearance. Non-enzyme-inducing AEDs did not result in changes in plasma concentration of brivaracetam, and brivaracetam did not alter metabolism of other AEDs. The same is true for oral hormonal contraception, in that neither brivaracetam nor oral contraception resulted in alteration of metabolism of the other (15).

### Use in Special Populations

Data on use of brivaracetam in pregnancy and while breast-feeding are not available. However, as mentioned previously, animal toxicology studies failed to reveal signs of abnormal fetal development, indicating that this medication may be safe in pregnancy. Age, gender, race, and renal function did not affect plasma brivaracetam levels. Plasma brivaracetam levels in elderly patients with severe renal impairment not requiring dialysis resembled those in nonelderly healthy patients. In patients with severe hepatic impairment, brivaracetam exposure increased by 50% to 60% compared to healthy controls and therefore use of this medication in that population should be limited or decreased (15).

### Pediatric Use

Brivaracetam use in pediatrics is not presently recommended. Studies are underway investigating the dose and efficacy of this medication in children aged 1 month to 16 years with generalized or partial-onset epilepsy. The estimated efficacious dose in this age group is likely going to resemble the adult dose at approximately 1–5 mg/kg/day.

## GANAXOLONE

### Indications

Ganaxolone is the 3B methylated synthetic analog of allopregnanolone currently undergoing Phase II trials in anticipation of applying for FDA approval for adjunctive

treatment of partial-onset epilepsy in adults and refractory infantile spasms in children. It is considered a neurosteroid and related to progesterone but is hormonally inactive.

### Dosing

Dosing for ganaxolone is still under investigation. Clinical trials have investigated doses of 900 mg/day to 1,500 mg/day in adults. In children, doses of up to 54 mg/kg have been used. It is administered twice a day (2).

### Pharmacology

Ganaxolone demonstrates two mechanisms of action depending on its concentration. At low doses, ganaxolone potentiates the action of gamma-aminobutyric acid (GABA) at GABA<sub>A</sub> receptors. With higher doses, it directly activates the GABA<sub>A</sub> receptors and prolongs opening of the Cl channel. Ganaxolone modulates both extrasynaptic and synaptic GABA<sub>A</sub> receptors. Activation of the extra synaptic receptors results in a persistent inhibition of neuronal excitability. Synaptic GABA receptor activation provides phasic inhibition (16). The extrasynaptic activity may be more important in cases of prolonged seizures and status epilepticus as synaptic GABA receptors may internalize with prolonged seizures, making them unavailable.

Ganaxolone is rapidly absorbed with  $T_{max}$  occurring 1.5 to 2 hours after ingestion. After high fat or high carbohydrate meals, ganaxolone absorption is decreased slightly. It is widely distributed and highly protein bound. It is extensively metabolized to mostly unidentified compounds by the CYP3A4 system. Excretion occurs primarily via the fecal route and only 20% excretion occurs through the kidneys (17). The plasma half-life is approximately 20 hours and no sex differences exist for metabolism of the medication. The drug exhibits linear kinetics with direct correlation between dosage and plasma concentration levels. Steady-state concentrations are achieved within 48 hours of ingesting medication.

### Efficacy Data

Efficacy of ganaxolone as adjunctive therapy in partial seizures in adults was evaluated in a Phase II study. A dose of 1,500 mg/day was compared to placebo. A significantly greater reduction of seizure frequency was noted with ganaxolone (18%) as compared to placebo (2%). In the open-label extension, over 90% of subjects continued participation and of those, the majority remained on the study drug throughout the entire 104-week period before tapering (2).

In the pediatric population, ganaxolone has been evaluated for treatment of infantile spasms. No significant difference was noted between drug and placebo in the primary end point, spasm cluster frequency. However, 17% of patients had a marked or moderate improvement in spasms with ganaxolone compared to 0% for placebo (15). Further investigations are planned on pediatric patients with infantile spasms.

### Efficacy in Other Conditions

Ganaxolone is currently being investigated as a migraine prophylaxis medication at doses of 750 mg/day. So far a significant therapeutic benefit has not been realized. Clinical trials using ganaxolone in mood disorders have been performed, but data are not yet available.

### Adverse Effects

In adults, the most common adverse effects of ganaxolone were dizziness, somnolence, and diarrhea. Serious adverse events occurred with the same frequency in the active treatment arm compared to the placebo arm. Other side effects included headache, convulsions, fatigue, fall, nasopharyngitis, dizziness, contusion, and nasal congestion (2). Weight change was not noted and vital signs or ECG changes were not observed in the clinical trials.

In children, the most commonly observed adverse events were somnolence, diarrhea, nervousness, and vomiting. Of note, one of the more concerning side effects seen in children is agitation, although occasionally behavioral improvement may occur as well (17).

### Toxicity, Overdose, and Contraindications

Toxicity studies on ganaxolone revealed the most common toxicity was dose-related, reversible sedation. With either single or multiple dosing of ganaxolone, target organ damage was not identified and hematologic and serum chemistries were not altered. Mutagenicity and carcinogenicity was not observed. In assessing CNS side effects in mice, ganaxolone had less interaction when coupled with alcohol than valproic acid did, and resulted in less cognitive impairment and ataxia. Maximum tolerated doses of ganaxolone in rodent studies were limited by sedation and/or liver weight gain associated with CYP induction. Continued toxicology studies reinforce the safety of ganaxolone with long term (15). Toxicology has not been determined in clinical studies.

### Warning and Precautions

Currently, there are no serious warnings or precautions in adults for ganaxolone. In pediatrics, agitation is a concerning side effect seen, but there do not appear to be any predisposing factors demonstrating predictability.

### Teratogenicity

Teratogenicity effects of ganaxolone in human are currently unavailable. In rats, however, up to 300 mg/kg/day failed to demonstrate any significant change in fetal development.

### Special Safety Concerns

Based on available studies, no serological monitoring is recommended for ganaxolone. Ganaxolone did not demonstrate

any changes in chemistry, hematology, vital signs, or physical and neurological examinations. ECGs remained stable throughout the treatment period.

### Drug Interactions

Ganaxolone is extensively metabolized by the liver with at least some metabolism occurring via the CYP3A4 enzyme system. It is not an inducer or inhibitor of this enzyme system. However, in vitro studies demonstrated reduced plasma concentration with coadministration of strong CYP3A4 inducers such as carbamazepine and phenytoin. Conversely, strong CYP3A4 inhibitors result in significantly increased plasma concentrations of ganaxolone, as demonstrated in an in vitro study using ketoconazole (17). However, in clinical studies for adult and pediatric populations, no significant interactions were noted, including in subjects concomitantly taking ganaxolone and one of the afore-mentioned drugs. In addition, no protein-binding interactions were identified with coadministration of valproic acid and ganaxolone despite ganaxolone's high level of protein binding.

### Use in Special Populations

Although no teratogenicity has been demonstrated in rats, no clinical trials have investigated ganaxolone's teratogenicity effects or its distribution in breast milk. Recommendations remain to avoid ganaxolone in pregnant women or women who are breastfeeding.

Only 20% of ganaxolone and its metabolites are excreted via the kidneys, and although there are no specific data addressing use of ganaxolone in renally impaired patients, it seems intuitive that at least mild-to-moderate renal impairment would not require dose adjustments. Alternatively, because of ganaxolone's extensive first-pass metabolism in the liver, moderate-to-severe liver impairment may limit its use in these patients.

### Pediatric Use

Ganaxolone is being evaluated for the treatment of refractory infantile spasms. Tolerated doses include up to 54 mg/kg/day, but with inconsistent results, as noted earlier. Additional studies are planned.

The list of the newest AEDs and investigational agents is constantly changing. Newer AEDs provide new mechanisms for controlling seizures, different efficacy, side effects, and pharmacokinetic profiles. For patients who have medically refractory seizures who are not candidates for surgery, having new AEDs available provides hope for better management. These new AEDs may not always bring better seizure control, but they may improve tolerability. Most importantly, they continue to offer hope. Epilepsy care providers must keep up to date with the latest available medication treatment options to best care for their patients.

**TABLE 29.1 Summary of Third-Generation AEDs**

**Eslicarbazepine**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
Adjunctive therapy for partial-onset seizures in adults	400 mg/day	800–1,200 mg/day	Unknown	Affects voltage-gated sodium channel	Dizziness, somnolence, headache, abnormal coordination. Unique side effect is diplopia	C	Diplopia, abnormal coordination, dizziness when combined with carbamazepine; second- or third-degree AV block is contraindication	Phenobarbital and phenytoin reduce eslicarbazepine concentration; hormonal contraceptives concentration reduced

**Brivaracetam**

Indication(s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
TBD	50 mg/day	100–200 mg/day	1–5 mg/kg/day	Enhanced affinity for SV2A and inhibitor of neuronal voltage-dependent sodium channels	Headache, somnolence, dizziness, and fatigue	TBD	Currently none	Increases the 10,11 epoxide metabolite of carbamazepine

**Ganaxolone**

Indication (s)	Starting Dose	Typical Dose Range	Pediatric Dosing	Mechanism of Action	Common Side Effects	Pregnancy Category	Warnings	Common Drug Interactions
TBD	800 mg/day	800–1,500 mg/day divided BID or TID	Up to 54 mg/kg/day	Modulates synaptic and extra synaptic GABA <sub>A</sub> receptors	Dizziness, somnolence, diarrhea	TBD	In pediatric populations monitor for agitation	In vitro increased clearance of ganaxolone with CYP3A4 inducers (carbamazepine, phenytoin) and decreased clearance with CYP3A4 inhibitors (ketoconazole; no clinically significant interactions in human studies)



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# Stimulation Therapy

*William B. Gallentine*

Despite the addition of numerous new antiepileptic drugs (AEDs) over the past 20 years, a substantial number of patients with epilepsy (approximately 35%) are unable to achieve pharmacologic seizure control. As such, nonpharmacologic options such as epilepsy surgery, ketogenic diet (KD), and neurostimulation are often pursued in these patients. Neurostimulation refers to the use of electrical stimulation to manipulate neural networks, resulting in a desired therapeutic effect. The FDA has approved two neurostimulators for the treatment of epilepsy: the vagus nerve stimulator (VNS) and a responsive neurostimulation (RNS) known as Neuropace®. The VNS received its initial FDA approval in 1997, and since then, over 50,000 devices have been implanted in both adults and children. The Neuropace device has been approved very recently, and there is much more limited experience with its use. More recently, another type of neurostimulation has been investigated, that is, deep brain stimulation (DBS). This is not yet approved for use by the FDA. The purpose of this chapter is to provide an overview of the various forms of stimulation therapy, with the main focus on VNS, as this is the device being most widely used in clinical practice.

## VAGUS NERVE STIMULATION

### Overview

The VNS is an electrical device that consists of a generator implanted subcutaneously, usually on the left side of the chest, and an electrode, which is wrapped around the left vagus nerve in the neck. The “pacemaker-like” generator delivers an intermittent electrical stimulus to the vagus nerve which then relays this electrical signal to the brain. The generators, which are programmed to deliver impulses at timed intervals, have undergone several revisions over the years in an effort to upgrade their battery life, size, and diagnostic capabilities. Depending on the settings used for therapy, most VNS batteries will often last 5 to 10 years. However, those patients whose generators are set at low off-times (“rapid cycling”) may get only 1 to 2 years of life from their battery before needing to be replaced.

### Implantation

The device is typically placed in the operating room most commonly by a neurosurgeon or an ENT surgeon. Placement is minimally invasive, and is most often considered out-patient surgery, with most patients discharged home the same day. There are two incisions made, one in the left chest, and the other in the left neck. The generator is inserted into a pocket in the chest, while the electrode in the neck is wrapped around the vagus nerve. The two are connected by a lead, which is tunneled under the skin. The procedure is typically performed under general anesthesia and typically is done in less than 1 hour. VNS placement is considered low-risk surgery, with greatest risk surrounding infection, which is thought to occur in less than 2% of cases.

### Indications

The FDA has approved VNS in adults and adolescents for the treatment of drug-resistant partial-onset seizures based on its pivotal E03 trial (1). It is approved for adolescents, age 12 years and older, as the pivotal study only included children down to this age. However, multiple prospective and retrospective studies demonstrating both safety and efficacy in much younger children have been subsequently published (2). As such, it is quite common for VNS to be placed in children under the age of 12 (1 year of age being the youngest implanted) (2). Although approved by the FDA only for partial-onset seizures, VNS has also been shown to be effective in generalized epilepsies (Table 30.1).

### Patient Identification and Pre-Implant Evaluation

The International League against Epilepsy (ILAE) defines drug-resistant epilepsy as the failure of two appropriately chosen and tolerated AEDs (whether as monotherapies or as combination) to control seizures for an adequate period of time. Once it has become clear that the patient is drug

**TABLE 30.1 Generalized Epilepsy Syndromes for Which VNS has Been Reported to be Efficacious**

Lennox-Gastaut syndrome (both tonic and atonic seizures)
Absence epilepsy
Dravet syndrome
Progressive myoclonic epilepsy
Infantile spasms
Tuberous sclerosis

resistant, further evaluation to clarify the potential treatment options for the patient should be considered. This includes MRI (if not done within the past 2 years) and video EEG (vEEG) monitoring for seizure characterization/localization. Findings from these studies are helpful in determining epilepsy surgery candidacy. The importance of vEEG monitoring cannot be stressed enough, not only to localize seizures with the potential for epilepsy surgery, but also to assure that the drug-resistant spells are actually epileptic in nature. Unfortunately, cases have been reported in which EEG monitoring was not performed, and VNS was implanted in patients with psychogenic nonepileptic seizures. In circumstances where vEEG is not an option, ambulatory EEG to confirm that the events are epileptic should be performed at a minimum.

Patients who are not surgical candidates and who routinely have prolonged seizures or frequent emergency department (ED) visits or hospitalizations related to seizures are particularly good VNS candidates. Quite commonly patients will see a decrease in seizure length, resulting in decreased need for hospitalization and rescue medications.

### Mechanisms of Action

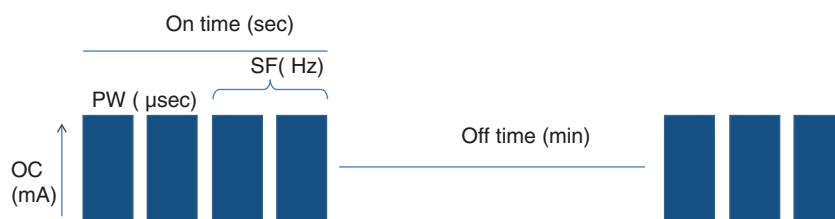
The definitive mechanism of action for VNS is unknown. Mechanisms likely involve interactions between the locus ceruleus, nucleus solitarius, thalamus, and limbic structures (3). Functional neuroimaging revealed activation of the cortex and thalamus during VNS stimulation. Animal models displayed changes in neurotransmitters, including elevation of norepinephrine, increased GABA, increased serotonin,

and decreased aspartate. VNS also has been shown to desynchronize EEG epileptic activity and decrease interictal discharges over time.

### Dosing

There are two adjustable modes for the device: the standard maintenance mode and the magnet mode. The standard maintenance mode provides the background settings that run throughout the day at the desired time frequency. The magnet mode provides on-demand stimulation, activated by a swipe of a magnet over the VNS, which may be used in an effort to abort a seizure. The magnet also provides a means for turning off the device. If the magnet is held over the device for more than 65 seconds and held there, the device will turn off until the magnet is removed.

The VNS has several different dosing parameters that can be adjusted, including output current (OC), signal frequency (SF), pulse width (PW), and signal on/off time (Figure 30.1). The OC represents the amount of electrical current delivered in a single pulse of stimulation (mA). OC may range from 0 to 3.5 mA and this is the setting most commonly adjusted in the first few months of VNS titration. Initial OC is usually 0.25 mA, with increases of 0.25 mA every 2 weeks, which is a reasonable time frame to observe for response. A typical goal OC setting is between 1.0 and 2.0 mA. Two adjustments to OC may be done on the same day for those patients who may not be able to come to a clinic every 2 weeks, depending upon patient tolerability. The SF is the number of impulses per second (Hz). The PW is the duration of each individual pulse within the stimulation period. On/off time is the amount of time the generator provides stimulation, and the amount of time between stimulations. The percent on time is referred to as the duty cycle. Changes in the on/off time often take a few months to see the desired effect, so a longer observation period is in order, as opposed to the 2 weeks usually observed when adjusting the OC. Tables 30.2 and 30.3 summarize the typical initial settings and suggestions for VNS dose titrations. There really are no incorrect ways to titrate, as patient tolerability is the most important factor. However, a conservative approach as suggested earlier will allow for the patients settings to be maximized and will likely result in less potential side effects and longer battery life.

**FIGURE 30.1** Adjustable VNS settings.

Abbreviations: µsec, microseconds; Hz, hertz; mA, milliamps; min, minutes; OC, output current; PW, pulse width; sec, seconds; SF, signal frequency.

**TABLE 30.2 VNS Dosing Suggestions****Initial Parameters:**

OC 0.25 mA, SF 20-30 Hz, PW 250-500  $\mu$ sec, on-time 30 sec, off-time 5 minutes, magnet current 0.5 mA, magnet on-time 60 seconds, magnet PW 250 to 500  $\mu$ sec.

**Follow up Titration:**

- Increase OC 0.25 mA every 2 weeks until a 50% reduction is seen up to 2.5 to 3.0 mA.
- If response is seen, maintain at current OC for the next 6 to 8 weeks to see if seizures continue to improve. If there is continued improvement, maintain the current settings.
- If no ongoing improvement is seen after 6 to 8 weeks, resume increasing OC by 0.25 mA every 2 weeks. If no improvement is seen after further dose increases up to 2.5 to 3.0 mA, reduction back to the OC at which a 50% seizure reduction was seen is reasonable.
- If no response is seen after 3 months of OC titration, reduction in the signal on/off time should be considered.
- Magnet current is typically set 0.25 mA higher than the baseline OC.

At this time, there are insufficient data to make evidence-based recommendations for dosing within the FDA-approved settings, as studies specifically designed to evaluate dosing have not been performed. In the limited studies that have been performed, no specific setting has been shown to be more or less effective as clinical improvement did not correlate with changes in OC, PW, SF, or signal on/off-time (4–6). In responders, higher dosing does not necessarily translate into a better response. As response to VNS seems to improve over time, in a patient who has responded with decreased seizure frequency and duration, continuing at the same settings for several months would be reasonable even if the settings are low. Some patients may have a therapeutic window at which they have the best response, which could be missed with aggressive dose titration. Continued dosing to higher settings in a patient who has already responded may also result in shorter battery life.

In a small subpopulation of nonresponders at standard settings, decreasing the signal off time (as low as 0.5 min) may result in improved seizure control (4). Decreasing the signal off time does substantially decrease the battery life. If there is no clear improvement in seizures after 6 months at the lower signal off time (less than or equal to 1.1, going back to the standard 5-minute off time is recommended to help prolong the battery life). Strategies to preserve battery life when “rapid cycling” would include lowering the SF to 20 Hz and PW to 250  $\mu$ sec. The most important consideration when dosing should be patient tolerability.

The magnet settings are typically 0.25 mA higher on the OC than the maintenance setting with a longer stimulation time of 60 seconds, and PW and SF are the same as the baseline settings. At seizure onset, the device may be activated with the swipe of the magnet over the device and repeated once per minute for the first 3 to 4 minutes of the seizure.

### Efficacy

#### *Standard and Magnet Mode*

In general, most studies show about 50% of patients have at least 50% reduction in seizure frequency at 1 year.

**TABLE 30.3 Suggested VNS On and Off-Time Dosing (Duty Cycle)**

- For patients with no response to standard setting (30 sec on, 5 min off) after 3 months of OC titration
- Stage 2: 30 sec on, 3 min off, observe for 6 to 8 weeks
- Stage 3: 30 sec on, 1.8 min off, observe for 6 to 8 weeks
- Stage 4: 30 sec on, 1.1 min off, observe for 6 to 8 weeks
- Stage 5: 21 sec on, 0.8 min off, observe for 6 to 8 weeks
- Stage 6: 14 sec on, 0.5 min off, observe for 6 to 8 weeks
- It is recommended to keep duty cycles under 50%
- If no response is seen under 1.1 min for more than 6 months, then return back to standard on/off-times.

Improvement in seizure frequency is typically not immediate but may occur slowly over 1 to 24 months. Many patients will see a substantial reduction in seizure duration. Unfortunately, only 10% to 15% become completely seizure free. However, for many patients a substantial reduction in seizure frequency can have a dramatic improvement in quality of life, even if they are still having some seizures. VNS efficacy is not dependent upon seizure type or etiology, thus it can be used for both generalized and focal-onset seizures. About 25% of patients are able to abort their seizures with magnet activation.

### *Children*

VNS usage in children with refractory epilepsy is quite common. Most studies report between 50% to 70% of children having at least 50% reduction in seizures. Side effects are similar to those seen in adults.

### *Quality of Life*

The majority of patients and families who undergo placement of VNS feel that the device in some way has improved their quality of life. For some patients, it is the reduction in seizure frequency. Many patients see their usage of rescue medication, as well as visits to the ED and hospitalizations, decrease dramatically. Level of alertness and cognition improves in the majority, even without changes to dosages



of medications. A few patients are even able to wean the number of their medications, but this is not often the case. The improvement in quality of life is often one of the biggest considerations when recommending VNS therapy.

### Adverse Effects

Side effects most commonly seen with VNS include hoarseness, cough, paresthesia, and shortness of breath. These are typically seen during stimulation and often may be improved by adjusting the dosing parameters. Adjusting the PW from 500 to 250  $\mu$ sec is the parameter that most often makes the biggest improvement in side effects. Decreasing the SF to 20 Hz may also help. Side effects are similar in both adults and children, and often improve over time. If a symptom occurs and it is unclear as to whether it is related to the VNS, turning off the device with the magnet to see if the symptoms resolve and then return when the device is turned back on can help clarify. Worsening of sleep apnea has been reported in some patients following VNS placement. As such, in patients considered high-risk for apnea (obesity, Arnold-Chiari malformation), polysomnography before and following placement of the VNS is reasonable.

### RESPONSIVE NEUROSTIMULATION

RNS (Neuropace®) is another device developed for the treatment of drug-resistant epilepsy that has recently obtained FDA approval. This device has diagnostic and therapeutic capabilities. It is aimed at those patients with drug-resistant epilepsy whose epileptogenic zone has been identified but cannot be resected because it involves eloquent cortex, and for those patients with bilateral foci. Recording electrodes are placed intraoperatively over the epileptogenic zones and are connected to the RNS device that is implanted in the skull. This device collects EEG data from the surface electrodes. After detection of an epileptic discharge, the device applies a brief electrical stimulus directly to the brain through the recording electrodes, which potentially aborts the seizure. Preliminary data revealed about 50% of patients had 50% reduction in seizures (7).

### DEEP BRAIN STIMULATION

DBS is an emerging treatment for drug-resistant epilepsy, but is currently awaiting FDA approval. The device consists of a generator, which like VNS is placed under the

skin on the chest, which provides intermittent stimulation to an electrode placed within the deep structures of the brain. Its mechanism of action is thought to be similar to VNS. Only the anterior nucleus of the thalamus has been adequately studied as a stimulation site for focal-onset seizures. In a recently released study, efficacy numbers were very similar to that seen with VNS, with 54% having at least 50% reduction of seizures at the 2-year follow-up, including some patients who had failed either VNS or epilepsy surgery (8). Twelve percent were free from seizure at 6 months. Other anatomic structures being studied for DBS in the treatment of epilepsy include the hippocampus, centromedian thalamic nucleus, caudate, mammillary bodies, locus ceruleus, and basal ganglia.

Stimulation therapy offers another viable treatment option for patients with drug-resistant epilepsy. VNS is a safe and effective alternative for both adults and children. Efficacy of VNS is not exclusively related to seizure control, but also improved quality of life. Over the next few years, the true utility of RNS will become evident as its clinical use increases. DBS therapy is on the horizon. Both RNS and DBS may be helpful in patients who have failed other forms of therapy, including VNS and epilepsy surgery.

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# Epilepsy Surgery

*Edgar Perez and Gerald Grant*

More than 2 million people in the United States have epilepsy, and 400,000 to 600,000 of them have seizures that cannot be controlled by antiepileptic drugs (AEDs) (1). A series on epilepsy management has shown a decreasing rate of seizure freedom with increasing AEDs. Approximately 47% of patients became seizure free on one AED, 13% on a second AED, and 1% on a third monotherapy. Only 3% were controlled with two AEDs and none with three (2). Epilepsy surgery is indicated for patients whose seizures are refractory to medication, defined often by two failed treatments of first-line medication and one combination therapy when used at therapeutic levels over 1 to 2 years. The goals of surgery are threefold: seizure control, minimal side effects from surgery, and improved quality of life. Unfortunately, unless the patient is seizure-free, the quality-of-life measures do not significantly improve. In general, surgical options include focal resection of epileptogenic cortex or disconnection of the epileptogenic cortex or network. Notably, only complete resection of the epileptogenic focus or lesion offers a possible cure.

## PREVALENCE OF SURGERY

In 1990, there were approximately 100,000 to 300,000 potential candidates for epilepsy surgery in the United States, yet surveys show that only 1,500 procedures were performed (3). Despite improvements in neurosurgical techniques and reports on its safety and efficacy, physicians and patients continue to misperceive surgical intervention as a last resort when, in reality, surgical therapeutic intervention has offered the best chance of cure. Examples of surgically remediable syndromes include:

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS)
- Focal epilepsy caused by discrete structural lesions that can be resected without introducing additional neurologic deficits
- Catastrophic unilateral or secondary generalized epilepsies of infants and young children that result from disturbances confined to one hemisphere, such as hemi-megalocephaly, Sturge-Weber syndrome, Rasmussen encephalitis

- Relatively large but unilateral developmental abnormalities, such as cortical dysplasias and porencephalic cysts.

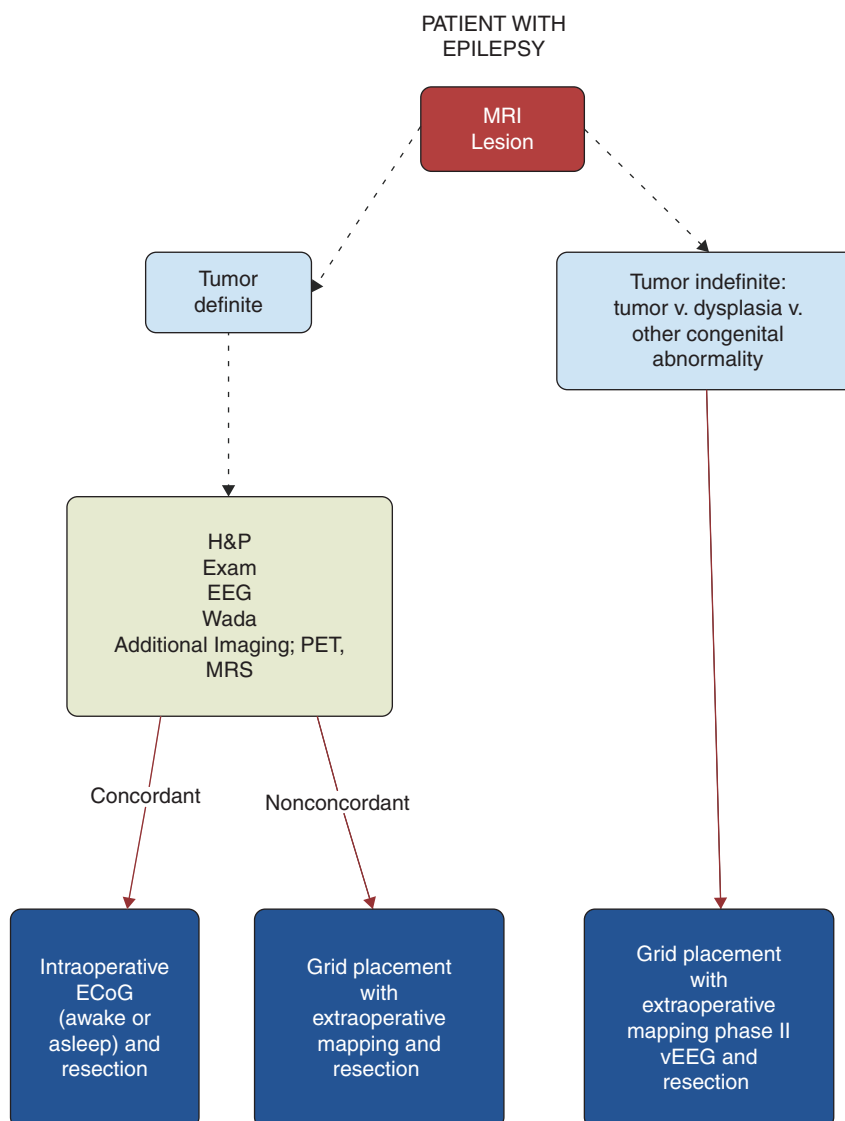
These conditions can be treated with anteromesial temporal lobectomy, localized cortical resection, hemispherectomy, hemispherotomy, or multilobar resection. The best results with respect to subsequent seizures, psychosocial readjustment, and quality of life are attained when surgery is performed as soon as it can be established that high-dose first-line AEDs as monotherapy have failed.

## SURGICAL EVALUATION PROCESS

The selection of candidates for epilepsy surgery has been discussed elsewhere in this textbook. Briefly, the following patient workup is usually done with each test providing a piece of information to assess for the possibility of surgical resection.

1. Medical history, including seizure semiology (type and frequency), antiepileptic drug history, daily functions and activities, quality-of-life assessment, and mood and behavioral assessment.
2. Comprehensive physical examination.
3. Brain MRI to investigate cerebral lesions and possible resectable lesions.
4. Video EEG (vEEG) monitoring to confirm the seizure type(s).
5. Functional MRI (fMRI) or magnetoencephalography (MEG) to determine language lateralization for temporal lobe cases.
6. Wada test (also known as an intracarotid amobarbital procedure, IAP) to predict memory dysfunction following a mesial temporal resection.
7. Ictal and interictal SPECT.
8. PET.
9. Neuropsychological evaluation.

Patients may require staged grid placement for language/motor mapping versus a single-stage intraoperative mapping session followed by surgical resection. See Figure 31.1 for a suggested algorithm of patient evaluation.



**FIGURE 31.1** Suggested algorithm for evaluation of a patient with refractory epilepsy and lesion on MRI.

### Presurgical Evaluation: MRI

Only MRI can demonstrate anatomic alterations associated with epilepsy, such as tumor, dysplasia, mesial temporal lobe atrophy or sclerosis, and gliosis. By EEG standard, MRI has a high specificity (78%–95%) and a low sensitivity (43%–55%) for epilepsy (4) (Tables 31.1–31.2). Though structural abnormalities are highly correlated with the epileptogenic focus, they are not synonymous. As such, MRI cannot be used alone to define an epileptogenic process, and is commonly used in conjunction with EEG for assessment.

Overall, MRI can be very helpful in the diagnostic workup of a patient with severe intractable epilepsy. The most common pathological substrate for temporal lobe epilepsy requiring surgery is mesial temporal sclerosis (MTS). However, moderate hippocampal atrophy and signal change can be missed. Conversely, extreme hippocampal changes,

especially on T2 and fluid-attenuated inversion recovery (FLAIR), may be erroneously called tumors when in reality they might represent severe sclerosis. It is important to keep this in mind when evaluating patients.

### Presurgical Evaluation: Wada Test

The Wada test is often used in presurgical patient evaluation to determine cerebral dominance for language and memory lateralization. Its use is controversial, but the goal is to reduce severe postoperative memory loss in patients who will undergo a unilateral resection of a temporal lobe. Specifics on Wada testing are discussed in Chapter 22. Briefly, amobarbital is introduced into the internal carotid arteries and injected into one hemisphere at a time. There is no universal, standardized memory test procedure for the Wada test, and the

**TABLE 31.1 Comparative Specificity and Sensitivity of Neuroimaging Procedures in Epilepsy (by EEG Standard)**

	TEMPORAL		EXTRATEMPORAL	
	SENSITIVITY	SPECIFICITY	SENSITIVITY	SPECIFICITY
PET	84%	86%	33%	95%
Interictal SPECT	66%	68%	60%	93%
Ictal SPECT	90%	77%	81%	93%
MRI	55%	78%	43%	95%

Source: From Ref. (5). Arora J, Pugh K, Westerveld M, et al. Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. *Epilepsia*. 2009;50(10):2225–2241.

task assessments as well as the techniques of injection vary across institutions. Having the patient name objects that are shown can assess language skills. Asking the patient to name as many objects as they can remember can assess memory. It is expected that the test will predict how well the patient's memory will function after a resection. Ideally, memory should not be impaired when the hemisphere of planned surgery is injected, thereby confirming adequate memory on the contralateral side. A score within two standard deviations of normal verbal memory ensures that the hippocampus can be safely resected without significant deficits.

Individual assessment of each surgical patient is recommended when deciding who should undergo Wada testing. At many clinical sites, Wada testing is being eliminated in cases in which the fMRI are highly lateralized. fMRI has been found to be in agreement with the Wada test in 91.3% of patients (5), and has the benefit of being noninvasive and providing within-hemisphere regional localization of function. However, care must be taken in using fMRI for language lateralization and sources of error must be considered. If the results from fMRI lateralization and neuropsychological testing are equivocal, as can be common in temporal lobe epilepsy, Wada testing is used to resolve the issue. Refer to Figure 31.2 for a suggested algorithm for determination of Wada testing. Though not all patients will need a Wada test, it is incorrect to always assume that a patient who is left-hemisphere dominant with right medial

temporal lobe epilepsy will not need it. Wada testing will depend on neuropsychological testing of the contralateral lobe. In this scenario, intraarterial studies would be indicated if neuropsychological testing showed poor verbal memory in order to ascertain that the patient has capacity for memory support if the dominant hippocampus is resected. Wada testing could be deferred if the patient has asymmetric memory, eg, poor memory on the ipsilateral side and spared memory on the contralateral side, and is noted to be clearly dominant on fMRI.

In general, memory impairment implicating the role of the contralateral hippocampus in cases with an apparently unilateral mesial temporal focus is a contraindication for surgical treatment. A patient with intractable epilepsy and temporal onset, and with a normal ipsilateral hippocampus and good memory is the patient at higher risk for memory decline following an amygdalohippocampectomy.

Drawbacks of the Wada test include: (a) a morbidity as high as 5% of causing a stroke due to the angiogram (6), (b) patient discomfort—many patients dislike the paralysis and speech arrest induced by the procedure; (c) an inability to localize speech or other primary language functions, and (d) a high cost.

### Decision Making and Indications of Substrate-Directed Surgery

Patients may undergo resection if the epileptogenic focus is concordant with other data (eg: imaging, vEEG results, PET, SPECT, neuropsychological testing, and MEG) and if that region can be safely removed without causing significant deficits. If the seizure focus overlaps with eloquent cortex, then multiple subpial transections can be considered. In cases showing generalized forms of epilepsy onset, surgery is commonly not recommended. However, in certain scenarios, such as in a child with drop attacks or atonic seizures, a corpus callosotomy may be beneficial, as will be discussed. All cases should be evaluated individually for risks and benefits, and be discussed at multidisciplinary epilepsy management team meetings.

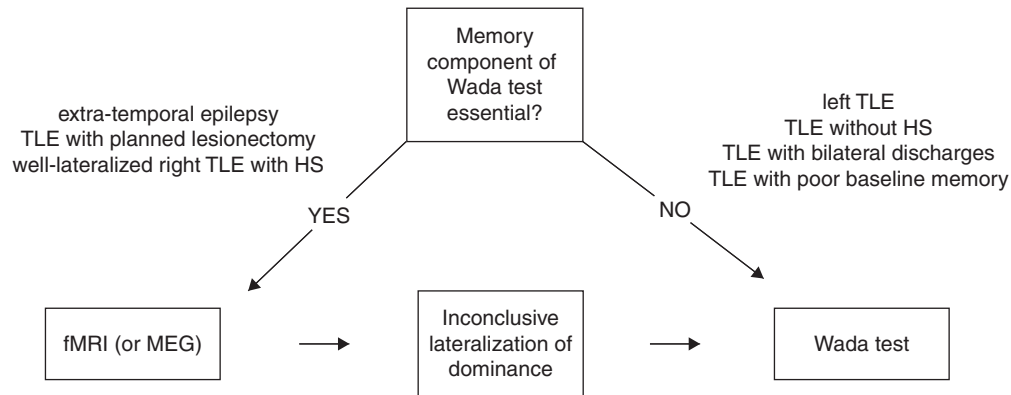
Substrate-directed surgery is indicated with concordant MRI substrate and EEG. Refer to Figure 31.3 for a suggested

**TABLE 31.2 Comparative Specificity and Sensitivity of Neuroimaging Procedures in Temporal Lobe Epilepsy (by Pathology Standard)**

	SENSITIVITY	SPECIFICITY
PET	81%	22%
Interictal SPECT	70%	36%
Ictal Spect	93%	13%
MRI	69%	68%

Source: From Ref. (5). Arora J, Pugh K, Westerveld M, et al. Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. *Epilepsia*. 2009;50(10):2225–2241.





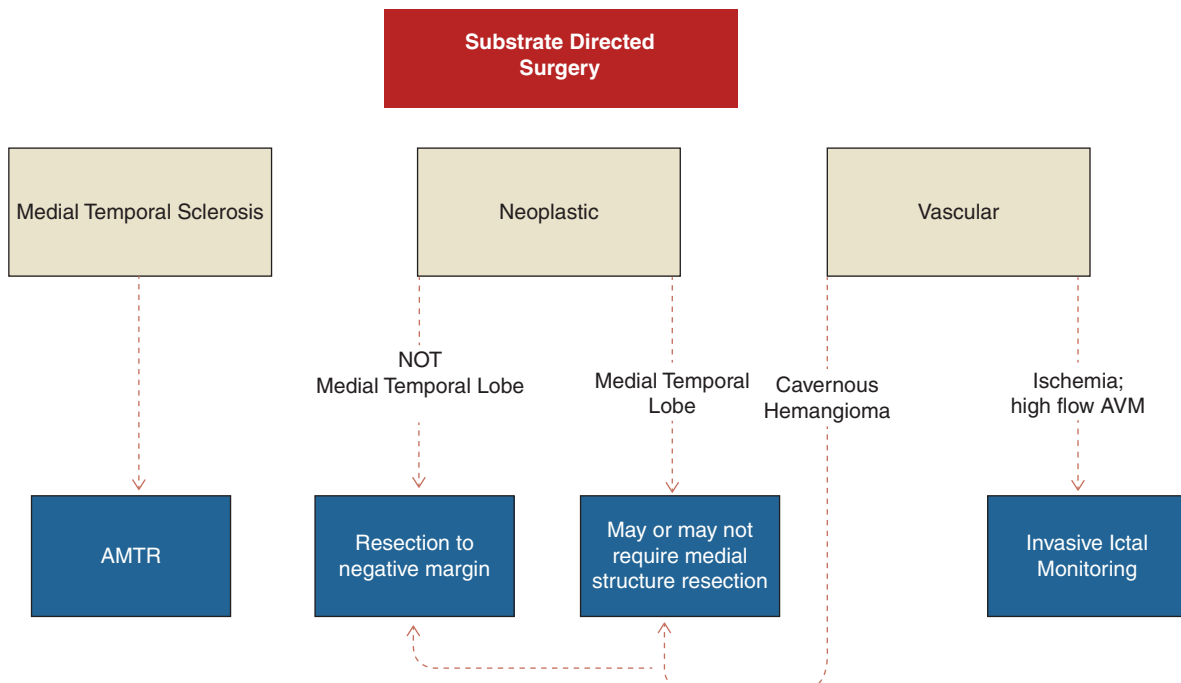
**FIGURE 31.2** Suggested algorithm for presurgical assessment of language dominance.

algorithm for substrate-directed surgery. If the medial temporal lobe is discovered to be the site of seizure focus, and it is in the nondominant hemisphere, anteromedial temporal resection (AMTR) is indicated. If the seizure focus is in the dominant hemisphere, AMTR would still be indicated if the patient passed their Wada test and it was felt that the patient's memory would be supported by the contralateral hippocampus.

Surgical resection of a neoplastic substrate is dependent on location. If the neoplasm is within the medial temporal lobe, the patient may require medial resection, including the hippocampus, for best seizure control. If it is a lateral tumor and the hippocampus looks normal, the hippocampus may be spared unless the workup reveals that the seizures originate there. If the tumor is found in any other lobar positions,

resection to the edge of the lesion or as defined by the EEG localization of the epileptogenic zone is indicated. The same paradigm holds true for cavernous hemangiomas, which are one of the most common forms of vascular lesions to cause medial lobe temporal epilepsy. Invasive ictal recordings with a grid in place may be helpful to safely resect arteriovenous malformations (AVMs) in eloquent cortex or in a patient with an AVM and refractory epilepsy.

In patients with dual pathology, eg, the presence of an extrahippocampal lesion plus hippocampal atrophy, resection of both the lesion and the medial structures is reported to be associated with improved outcomes than either alone (7). In a study on surgical outcomes for dual pathology epilepsy, lesionectomy plus mesial temporal resection resulted in complete freedom from seizures in 73% patients, while



**FIGURE 31.3** Suggested algorithm for substrate-directed surgery.

only 20% patients who had mesial temporal resection alone and 13% who had a lesionectomy alone were seizure free (7). An intracranial study to verify dual pathology, especially in the case of the dominant temporal lobe, is important in order to preserve functionally intact medial structures.

In general, invasive ictal monitoring (grid placement) is indicated if there is no MRI substrate or if there is discordance of substrate and scalp EEG. Bifrontal and temporal strip electrodes may be placed first if the seizures are not well lateralized. Once the seizures are well lateralized and are concordant with the imaging and other modalities, a craniotomy is performed to place a grid electrode for intracranial EEG monitoring to define ictal onset, followed by resection of the focus at the time of the grid removal 7 to 10 days later. Notably, there is a lower threshold for intracranial monitoring in cortical dysplasia because, although one sees MRI T2 signal change on FLAIR imaging, the epileptogenic zone can often be much larger. Studies in cortical dysplasia have shown that there is a higher success of seizure freedom if intracranial monitoring is done to determine the ictal onset, which determines the true epileptogenic zone. In one series, completeness of excision of cortical tissue displaying ictal or continuous epileptogenic discharges (I/CEDs) correlated positively with surgical outcome. Three-fourths of the patients in whom it was entirely excised had either complete seizure freedom or reduction by greater than 90% of major seizures; in contrast, uniformly poor outcome was observed in patients in whom areas containing I/CEDs remained in situ (8). Other structural defects are critical to resect along with ictal onset. For example, if seizure onset is at the edge of an area of cortical dysplasia, the pathological substrate plus the region of ictal recording should be removed.

### INTRACRANIAL ELECTRODE STUDIES

Intracranial electrodes help lateralize the seizure focus, and also help in brain mapping of eloquent areas. There are four main clinical scenarios that are likely to require an intracranial study.

1. Patients who harbor dual pathology, nonlesional epilepsy, extratemporal epilepsy, and lateral temporal lobe epilepsy will frequently require intracranial electrodes to map the epileptogenic focus using electrocorticography (ECoG) and the adjacent functional cortex using cortical stimulation (9).
2. Patients with bilateral independent temporal lobe spikes or bilateral MTS will require intracranial electrodes to lateralize the dominant epileptogenic temporal lobe and improve the success for postoperative seizure freedom (10). Once laterality of seizure onset has been determined, the patient may then be a candidate for placement of grid and additional strip electrodes. However, bilateral craniotomies for grid placement are not routinely performed due to the surgical morbidity.
3. Patients whose workup is discordant or inconclusive may require intracranial electrodes for further monitoring and assessment (11).

4. Young patients who are unable to tolerate awake cortical mapping for resection of their tumor may require intracranial electrodes for extraoperative mapping.

### Intracranial Electrode Placement

If an intracranial study is indicated, the placement of intracranial electrodes is guided by the results of Phase-1 presurgical evaluation, including scalp vEEG recording, MRI, and other imaging. Electrodes are inserted through 5-mm burr holes placed both frontally and temporally on both sides of the brain. Most often, anterolateral and posterolateral temporal electrodes are inserted in addition to a subtemporal electrode. Preference of strip electrodes and depth electrodes depends on the epilepsy center and experience of the team. (See the following for advantages and disadvantages of the different electrode types.) A frontal burr hole may be considered if there is a suggestion of orbitofrontal involvement or rapid spread to the frontal lobe. The frontal burr hole, made just behind the hairline and parasagittal, is used to place three frontal strips: lateral, anterior subfrontal, and interhemispheric. For extraoperative ECoG, the electrodes are sutured along their border to the edges of the dura to avoid displacement during the monitoring period, and the dura is then closed in a "water-tight" fashion.

#### Strip Electrodes

A strip electrode is a single linear array of disk electrode contacts. See Figure 31.4A

*Advantages.* Strip electrodes do not penetrate the cortex and are surface based. Multiple strip electrodes can be placed through a burr hole, requiring less operative time. They can be used for extraoperative cortical stimulation to map out functional areas of the brain.

Maneuvers using strip electrodes can facilitate recording from specific regions: (a) a strip advanced around the temporal pole and underneath the lesser wing of the sphenoid bone will follow the medial temporal lobe contour, and invariably end up along the medial basal temporal lobe surface, allowing adequate coverage of the parahippocampal gyrus along its long axis extending posterior to the level of the collicular plate (12); (b) a strip advanced along the posterior temporal lobe in the posteromedial direction is guided by the surrounding dural structures including tentorium, and invariably ends up at the occipital interhemispheric space. This strip allows for medial occipital recording or cortical stimulation of the visual cortices. In addition, this strip samples the basal surface of the posterior temporal and occipital lobes (13).

*Disadvantages.* Strip electrodes cannot record deep brain structures. In addition, placement can be unpredictable and inaccurate by virtue of the insertion technique and experience of the surgeon (14).

### Depth Electrodes

A depth electrode is a thin wire that can be placed in deep brain structures.

*Advantages.* Depth electrodes help to determine laterality. They can record from deep brain structures. Three depth electrodes are often placed from lateral to mesial to record from the amygdala, anterior, and posterior hippocampus.

*Disadvantages.* There is a 2% to 3% risk of an intracerebral hemorrhage (potentially due to burr hole placement with parietal-occipital burr hole trajectories avoiding the multiple convolutions of the temporal lobe where major branches of the middle cerebral artery (MCA) can be found, and minimizing bleeds) (15). Only one depth electrode can be placed per twist drill hole. In addition, depths are associated with longer operative times and increased cost due to the use of stereotactic equipment for placement. *Note:* histopathology of resected tissue reveals needle track evidence with gliosis and inflammation from depth electrode placement. However, this pathology is believed to be clinically insignificant, and there is no published evidence supporting permanent cognitive dysfunction.

### Grid Electrodes

A grid electrode is an array of parallel rows of disk electrode contacts (see Figure 31.4B).

*Advantages.* Grids have the ability to localize seizure focus and conduct language and motor mapping. Grids give ample coverage of language sites as well as face and hand motor areas.

*Disadvantages.* Grids necessitate a large craniotomy and increase the risk of a subdural hematoma (15).

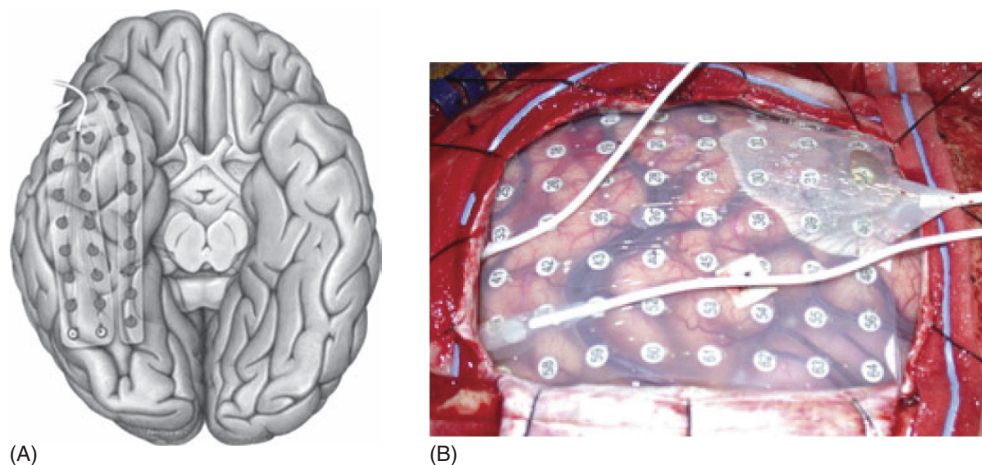
### Electrocorticography

Subdural recordings are associated with a higher sensitivity for detecting epileptiform discharges than scalp EEG. There are two types of intracranial ECoG, intraoperative ECoG and extraoperative ECoG. For intraoperative ECoG, the electrodes are placed on the brain during a surgical procedure to remove a lesion causing epilepsy, and are removed at the end of the surgery. This procedure is only done in the operating room. For extraoperative ECoG, the electrodes are placed in or over the brain in areas suspected to be epileptogenic foci, and are left in place. The patient is then brought back to the ward where recordings are made to capture seizures. The electrodes are removed at a later date.

#### Intraoperative Electrocorticography

Intraoperative ECoG offers flexible placement of recording and stimulating electrodes, the ability to directly stimulate regions of the brain to determine which parts to spare, and the ability to assess the presence or absence of interictal epileptiform activity immediately pre- and postresection. However, intraoperative ECoG has limitations, including limited sampling time, exclusive interictal spikes and sharp wave recordings, and a lack of seizure (ictal) capture. It is also impossible to distinguish primary epileptiform discharges from secondarily propagated discharges arising at a distant epileptogenic site. In addition, background activity and epileptiform discharges may be altered by the anaesthetics and/or narcotic analgesics required by the surgery itself.

While the use of intraoperative ECoG in resection surgery has been an accepted clinical practice, recent studies have shown that the usefulness of this technique varies on the patient's type of epilepsy. Studies suggest a critical value of intraoperative ECoG in lesion-related frontal lobe epilepsy (17), lesion-related temporal lobe epilepsy (18,19), subpial transections, and cortical dysplasias (8,20). However, it has been found impractical in the standard resection



**FIGURE 31.4** (A) Strip and (B) grid electrode.

Source: From Refs. (13)A; and (16)B.

of MTLE with MRI evidence of MTS. In a series involving resections with intraoperative ECoG, there was no correlation between residual spikes on pre- and postresection ECoG and outcome. These findings do not support the role of intraoperative ECoG in guiding standard mesial temporal lobe resections (18). Finally, the added impact of interictal spike frequency measures was modest, if any, in cases with available ictal ECoG and neuroimaging (21). However, although chasing spikes has not been proven to improve outcome following surgery, it may still be done for prognostic reasons since residual spikes may be a poor prognostic feature.

#### *Extraoperative Electrocorticography*

In the absence of an observable lesion to direct the surgical intervention, centers often rely on more extensive ECoG or on extraoperative ECoG monitoring to map the ictal onset prior to cortical resection. The seizure onset zone can be determined only after a seizure occurs; thus, some patients may have to undergo monitoring for more than a week until they experience a seizure. A typical intracranial monitoring study lasts 4 to 10 days postoperatively. Benefits and risks must be assessed in lengthier monitoring periods since a recording period of more than 10 days may increase the risk of complications, including infection (22), and increase the total medical cost.

Ictal ECoG recordings during extraoperative monitoring are visually reviewed daily to determine the electrode contacts where the seizures begin. Seizure onset is defined as a sustained rhythmic change on ECoG accompanied by subsequent clinically typical seizure activity, not explained by state changes, and clearly distinguished from background and interictal activity. Unfortunately, the placement of electrodes alters the normal electrical environment of the brain, potentially leading to temporary cessation of seizures or alteration of a patient's habitual seizure semiology. As a result, it is important to confirm that the recorded seizures during an intracranial study are similar to the patient's habitual seizures and even consider reducing the antiepileptic medication prior to surgery in a patient with rare intractable seizures.

### **TECHNIQUES AND TYPES OF SURGICAL RESECTION**

The basic technique for resection of epileptogenic tissue involves coagulating the surface or pial vessels, sharply incising the pial membrane covering the cortex, and using fine suction or bipolar cautery to dissect through the gray matter tissue down to white matter. Care is taken to not resect more than needed to preserve the white matter tracts as long as they are not involved in the functional epileptic network. There are several types of surgical procedures that can be performed to treat epilepsy. These include temporal lobectomies, lesionectomies (resection of MRI evident abnormal brain tissue), corpus callosotomies, hemispherectomies, and multiple subpial transections (MST).

### **Temporal Lobectomy**

Temporal lobectomy is the most common surgical procedure performed for medically refractory epilepsy. A standard lobectomy consists of the removal of the entire temporal lobe, including the mesial structures; however, this is rare today. Currently, temporal lobectomies involve a more limited resection in order to try to conserve as much neuropsychological function as possible. There are two main types of temporal lobe surgeries for epilepsy: AMTR and selective amygdalohippocampectomy (SAH), of which there are three main surgical approaches that will be discussed.

#### *Standard Anterior Temporal Lobectomy*

In a standard anterior temporal lobectomy (ATL), resection of the lateral temporal structures allows for visualization of the mesial structures and removal of the hippocampus.

Briefly, the patient is supine with the ipsilateral shoulder elevated. The head is lateral with the zygoma at a 10-degree angle from the horizontal plane. A craniotomy is performed on the frontal bone posterior to the pterion. A posterior cortical incision at the lateral temporal gyri begins approximately 5.5 cm from the temporal tip on the nondominant hemisphere and 4.5 cm from the temporal tip on the dominant side at the level of the middle temporal gyrus. Posteriorly and inferiorly, the dissection continues down to the level of the collateral sulcus. The dissection then continues anteriorly to the anterior tip of the temporal lobe and laterally to the floor of the middle fossa. The anterolateral temporal lobe is removed. The white matter is dissected along an imaginary plane to identify the temporal horn of the lateral ventricle, which is usually at the intersection of the plane of the collateral sulcus and superior temporal sulcus. The parahippocampus that includes the uncus is then resected subpially followed by an amygdalohippocampectomy.

#### *Anteromedial Temporal Resection*

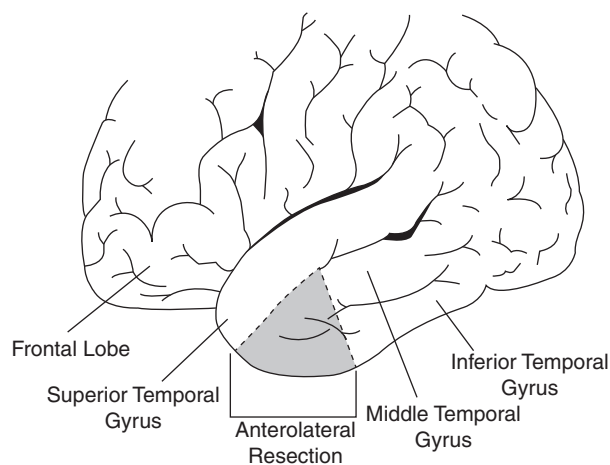
In the 1980s, a modified approach, AMTR, was introduced for temporal lobectomies for patients with medial temporal ictal onset, such that all of the medial structures are removed via a limited temporal pole resection, sparing the superior temporal gyrus.

The resection involves a 3- to 3.5-cm neocortical resection of the pole, including the middle and inferior temporal gyrus, as access to the temporal horn, facilitating the resection of the important structures that provide the triad for epileptogenesis in the medial temporal lobe, namely the entorhinal cortex, the amygdala, and the hippocampus (Figure 31.5).

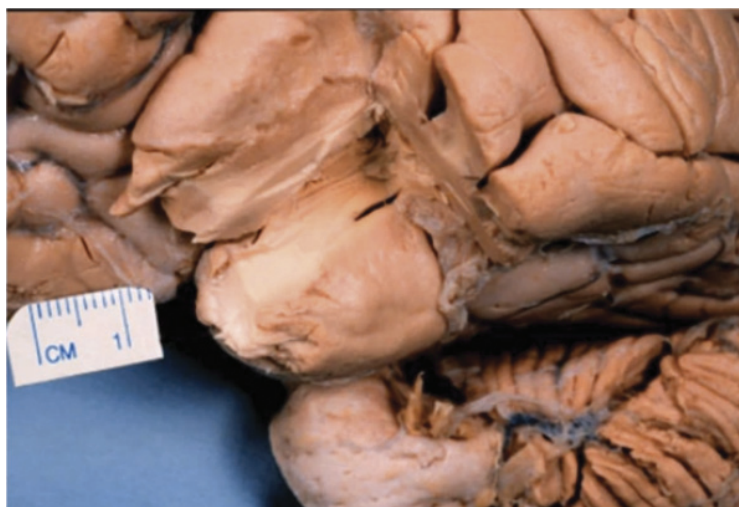
Briefly, the patient is positioned supine with the head extended 50 degrees backwards towards the ipsilateral shoulder; this head extension is critical to throw the hippocampus into a perfectly aligned view giving microscopic exposure of the hippocampal tail. A curvilinear incision is made in order to expose a sizeable portion of the temporal lobe: the posterior skin incision is at the point of the mastoid vertex and the anterior curve is at the anterior hairline. The skin and



# ANTEROMEDIAL TEMPORAL LOBECTOMY LATERAL VIEW



(A)



(B)

**FIGURE 31.5 AMTR.**

Source: From Ref. (23). Spencer D. Medial Temporal Lobe Epilepsy: Evaluation. In Cohen-Gadol A, ed. *ANA: Grand Rounds Video Conference*. 2013.

temporalis muscle are elevated as a single flap and reflected anteriorly. A standard craniotomy is done, exposing the posterior temporal neocortex. This exposure allows for lateral mobilization of the temporal neocortex in order to visualize the posterior tail of the hippocampus later in the procedure. The inferior temporal pole resection involves 3.5 cm of middle and inferior temporal gyrus. The first corticotomy is conducted along the superior temporal sulcus by coagulating pia and cutting across. Preservation of the vein of Labbé is important. In addition, the superior temporal gyrus is not violated. The lateral temporal neocortex is removed from the superior temporal sulcus using arachnoid of fusiform gyrus and middle fossa protuberance as landmarks. This technique helps the surgeon keep out of the temporal stem, which has no landmarks. The center of the middle temporal gyrus is then used as a landmark to open the ventricle lateral to the hippocampus without injuring it. A small part of the ventricle is opened. A white matter dissection is done along the occipital temporal fasciculus, mobilizing the temporal lobe laterally to see around the hippocampus.

An imaginary line drawn between the turn of the MCA, or approximately the MCA bifurcation, and the anterior edge of the choroid plexus in the temporal horn, the inferior choroidal point, forms a reliable landmark for defining the superior extent of resection during removal of the amygdala (24). The amygdala can then be removed in a selective manner. Once the amygdala is removed, the third nerve is found underneath the arachnoid to ensure that the amygdalotomy is complete. Afterward, the choroid plexus is disconnected from the hippocampus and care is taken to avoid injuring the anterior choroidal artery at the choroidal point in the ventricle. Then, the hippocampus and parahippocampus are undermined from the arachnoid over the basal cisterns.

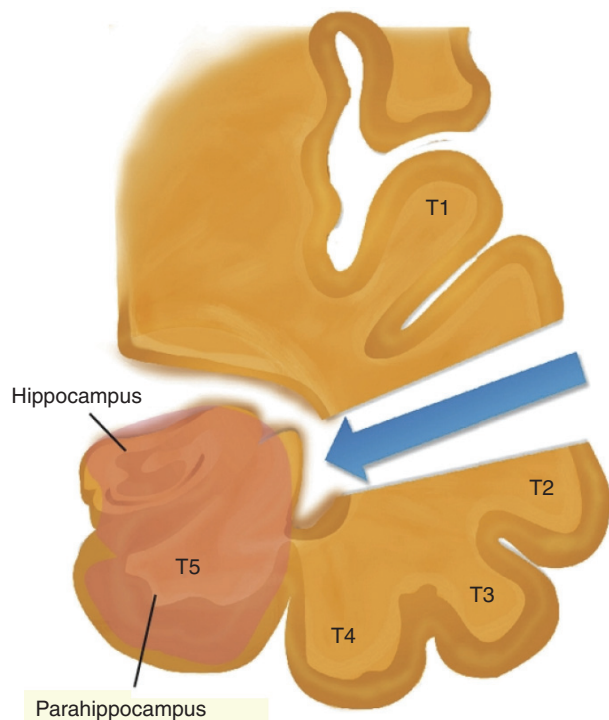
## *Selective Amygdalohippocampectomy*

In SAH, the neurosurgeon resects the medial temporal structures, including the amygdala and the hippocampus, but leaves the lateral temporal lobe intact. The rationale for SAH has been that it should provide equivalent seizure control because the mesial structures, the presumed source of the seizures, are removed with limited damage of the lateral temporal neocortex and the underlying white matter, possibly better preserving neurocognitive functions. This is becoming a common temporal resection performed at many centers.

Niemeyer proposed the SAH in 1958 using a *transcortical* incision through the middle temporal gyrus (Figure 31.6). In 1985, Yasargil and Wieser advocated an SAH with a different approach, the *transsylvian* approach through the deep Sylvian fissure. Hori (25), Park (26), and Little (27) have also described variations of the SAH using a *subtemporal* corridor. In this approach, the amygdala and hippocampus are removed through an opening in either the fusiform or parahippocampal gyrus.

These approaches have been shown to result in similar favorable seizure-freedom outcomes. Better cognitive outcomes have been suggested with the transsylvian SAH since there is less collateral neocortical damage. In general, the main complications in SAH are vascular injuries.

*Transcortical approach.* This approach involves a craniotomy centered on the projection of the middle temporal gyrus, followed by a longitudinal cortical incision through the middle temporal gyrus. An alternative approach is through the anterior superior temporal gyrus. The surgeon may use neuronavigation devices to direct the dissection to the temporal horn of the lateral ventricle. Once in the ventricle,



**FIGURE 31.6** Transcortical approach.

Source: From Ref. (28). Al-Otaibi F, Baeesa SS, Parrent AG, et al. Surgical techniques for the treatment of temporal lobe epilepsy. *Epilepsy Res Treat.* 2012;2012:374848.

the choroid plexus with the choroid point is identified. Subsequently, the uncus is emptied, and the amygdala and hippocampus are disconnected from the surrounding structures and removed subpially.

**Disadvantages:** a portion of the lateral temporal neocortex must be dissected.

**Transsylvian (Yasargil) approach.** The surgeon performs a pterional craniotomy of approximately 5 cm in diameter followed by microsurgical dissection of the sylvian fissure (2.5–3 cm). The surgeon reaches the temporal horn of the lateral ventricle via the inferior limiting sulcus. Once in the ventricle, the surgeon resects the mesial structures as described earlier.

**Advantages:** This approach avoids injury to the temporal neocortex and underlying white matter, which are traversed in the transcortical approach. It also allows *en bloc* resections. The transsylvian approach has been suggested to transect fiber pathways important for seizure propagation, leading to better seizure outcomes; but this has not been confirmed.

**Disadvantages:** The transsylvian approach is technically difficult due to a limited (2–2.5 cm) cortical incision and the presence of major blood vessels in the sylvian fissure. There is a greater chance of injuring the M1 portion of MCA within the sylvian fissure. There is also inevitably injury to the superior temporal, inferior temporal, and fusiform gyri (29).

This approach results in transection of the temporal stem, usually by approximately 20% (30).

**Subtemporal approach.** This approach involves opening the temporal horn from the basal surface of the temporal lobe, thereby sparing the lateral neocortex and temporal stem, which are affected in a traditional transsylvian approach.

**Advantages:** The subtemporal approach preserves functional temporal lobe tissue in the superior, middle, and inferior temporal gyri. It does not disrupt frontotemporal white matter pathways that reside within the temporal stem. In addition, the visual fibers near the roof of the temporal horn are spared, avoiding visual field defects. It might produce fewer neuropsychological sequelae, though data are insufficient to make this claim (31,32).

**Disadvantages:** It may require excessive retraction of the temporal lobe and removal of the zygomatic process. It may result in injury to the vein of Labbé.

### **Selective Amygdalohippocampectomy Versus Anterior Temporal Lobe Resection**

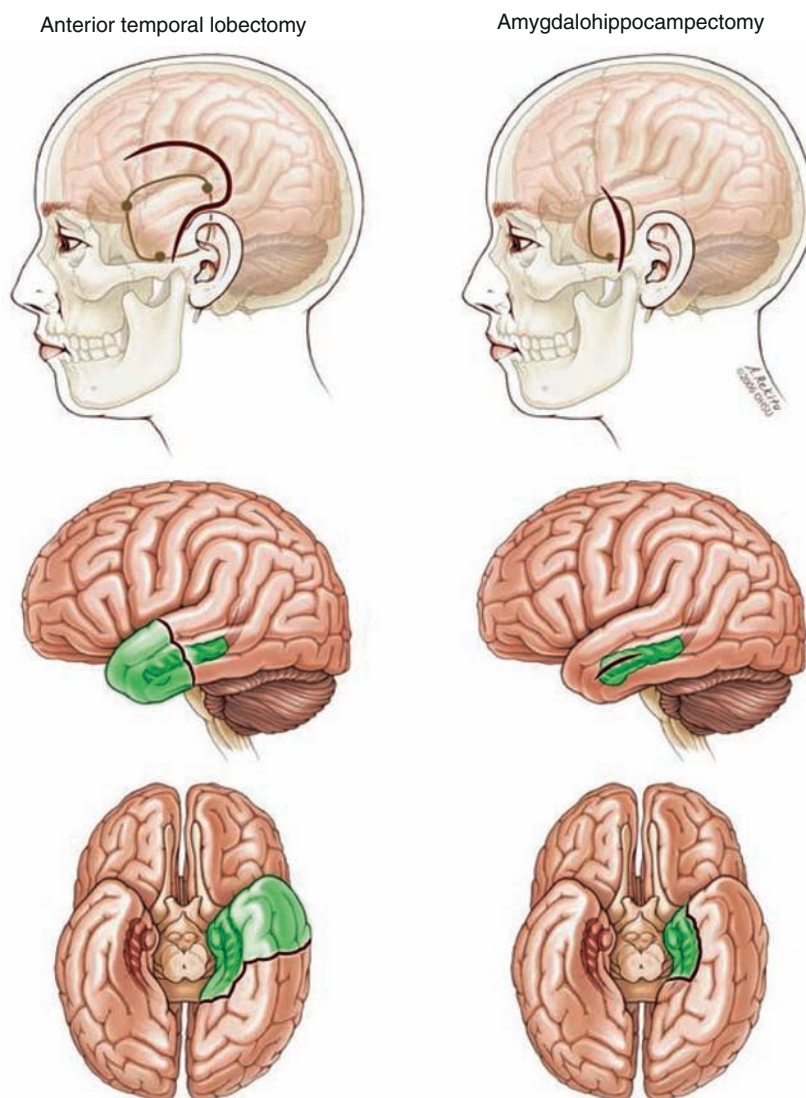
The efficacy of SAH versus ATL remains controversial. Refer to Figure 31.7 for a visual comparison of anterior temporal lobectomy and selective amygdalohippocampectomy. A literature review concluded that patients who underwent an SAH have similar seizure outcomes and better cognitive outcomes than those who underwent an ATL resection (33). Since SAH is also less invasive, this procedure has become popular in most centers. However, a 2013 literature review and meta-analysis of data showed a modest but statistical difference between ATL and SAH, with 8% more patients with MTLE becoming seizure free after ATL (34). Given the limited quality of evidence, neither SAH nor ATL resections can officially be recommended over the other option as a standard or guideline for the surgical management of TLE.

### **Anatomic Considerations in Temporal Lobectomy**

Anatomical structures/landmarks considered in a temporal lobectomy include Wernicke's area (if dominant hemisphere), optic radiations (if non-dominant hemisphere), the Sylvian fissure, and the incisura.

In a temporal lobectomy of the dominant hemisphere, the surgeon is careful to preserve Wernicke's speech area. Classically, dominant hemisphere anterior temporal cortex in the middle and inferior temporal gyri are not considered essential for language. There are visual and auditory naming areas however in the middle temporal gyrus on the dominant side. The line of the central fissure or the vein of Labbé, located 4 to 5 cm from the temporal tip, has been proposed as the posterior limit of the "safe" zone. It is usually safe to resect up to 4 to 5 cm from the temporal tip.

If the temporal lobectomy is performed on the nondominant hemisphere, the surgeon is most concerned with the optic radiations, which contain all the visual fibers of the opposite half of the visual field. The optic radiations course anteriorly



**FIGURE 31.7** Comparison of anterior temporal lobectomy and selective amygdalohippocampectomy.

Source: From Ref. (35). Spencer D, Burchiel K. Selective amygdalohippocampectomy. *Epilepsy Res Treat.* 2012;2012:382095.

over the roof of the inferior horn, then backward, forming the Meyer's loop. Transections of fibers in Meyer's loop can lead to superior homonymous quadrantanopia, which may be acceptable and does not disturb the patient in daily life.

### Corpus Callosotomy

The corpus callosum is the most important pathway for rapid interhemispheric spread of epileptic activity (36). The simple premise of a corpus callosotomy is that severing the connections between the hemispheres will stop the spread of seizures. In addition, the theory is that if neurons in both hemispheres are required for seizure onset, then severing them might also help reduce seizure frequency. Importantly, the goal of a corpus callosotomy is palliative, not seizure freedom. This surgery is indicated for patients who are medically refractory and who are not candidates for a focal resective

surgery and include: (a) patients with drop attacks that lead to injuries (b) patients with generalized seizures involving unilateral hemisphere damage, and (c) some patients with generalized seizures without an identifiable, resectable focus.

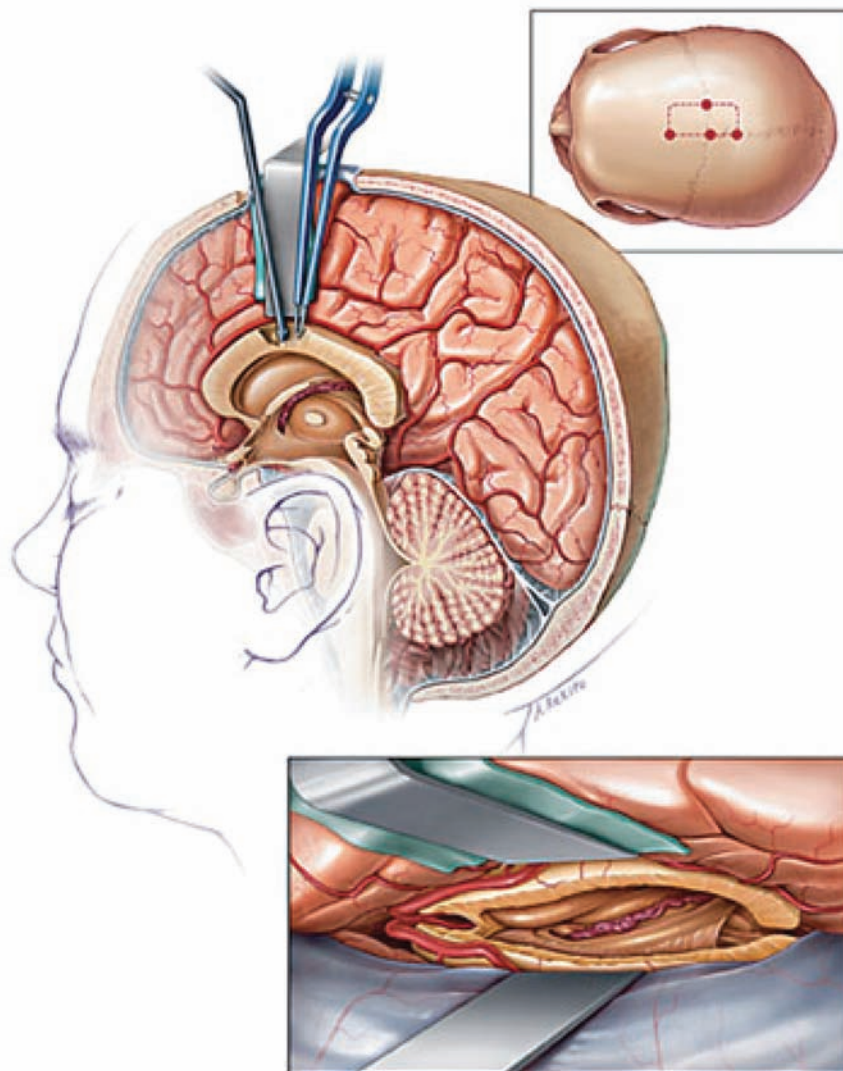
### Surgical Technique

A bifrontal craniotomy is performed, and via an interhemispheric approach an anterior 2/3 callosotomy or full callosotomy is generally performed. Image guidance can be helpful to delineate the extent of the callosotomy. The two pericallosal arteries lie directly over the callosum and should be protected and avoided (Figure 31.8).

### Outcomes

The chance of seizure freedom after a corpus callosotomy is only 10%. So this procedure is primarily for patients who





**FIGURE 31.8** Callosotomy approach.

Source: From Ref. (37). Rahimi SY, Park YD, Witcher MR, et al. Corpus callosotomy for treatment of pediatric epilepsy in the modern era. *Pediatr Neurosurg.* 2007;43(3):202–208.

might benefit from reduced risk of injuries from seizure reduction, such as those with drop attacks who fall a lot and need to be in a helmet for safety. Therefore, the procedure is only meant to be palliative. Even drop attacks are not completely eliminated. A meta-analysis shows that in the long term (>5 years), only 35% of patients are drop-attack free (38).

Based on outcome studies, the benefits of a corpus callosotomy are as follows: seizure reduction, reduced risk of injury, improved overall daily function, and family satisfaction. Subsequent quality of life is difficult to assess because patients often present with severe mental retardation or developmental delay, and family satisfaction has been increasingly used as a surrogate marker. Notably, corpus callosotomy is associated with low morbidity.

The outcome for drop attacks is more likely to be favorable if the patient has clinical, radiologic, or EEG evidence of a unilateral lesion. True generalized slow spike and

wave activity, characteristic of Lennox-Gastaut syndrome, is also associated with a favorable outcome. The presence of independent bilateral spikes on preoperative EEG and severe mental retardation are associated with unfavorable outcomes, especially for drop attacks.

#### *Anterior Corpus Callosotomy Versus Complete Corpus Callosotomy*

In an anterior 2/3 callosotomy, the splenium is spared to preserve sufficient fibers for interhemispheric transfer of some perceptual information and to diminish the risk of disconnection syndrome. However, the chance of a callosotomy exhibiting a significant impact on the quality of life of patients tends to be proportional to the extent of the disconnection (39). The complete arrest of drop attacks (atonic and tonic seizures) may be observed in up to 91% of pediatric



cases by total callosotomy, but only in 67% by partial section. In terms of neurologic complications, the frequency is nearly equal in partial and complete resections; however, complication severity is comparatively less in partial resections (40). Case series have shown a stronger association of disconnection syndrome after complete callosotomy versus partial (40). A literature review reported split-brain syndrome in 33% of patients after total or near-total callosotomy, with 30% of the cases transient and 3% persistent (41).

### Complications

Complications of corpus callosotomy include disconnection syndrome, language impairment and transient aphasia, transient akinetic state, memory deficits, mild neuropsychological impairment, new types of seizures, aseptic meningitis/ventriculitis after exposure of the third ventricle, transient neurological deficits, permanent neurological deficits, and death.

### Disconnection Syndromes

Disconnection syndromes can occur following complete corpus callosotomies. These syndromes are characterized by the absence of interhemispheric relay of information from a stimulus presented unilaterally. In general, the separated hemispheres are unable to share information about stimulus identity, shape, and higher-order associations (42,43).

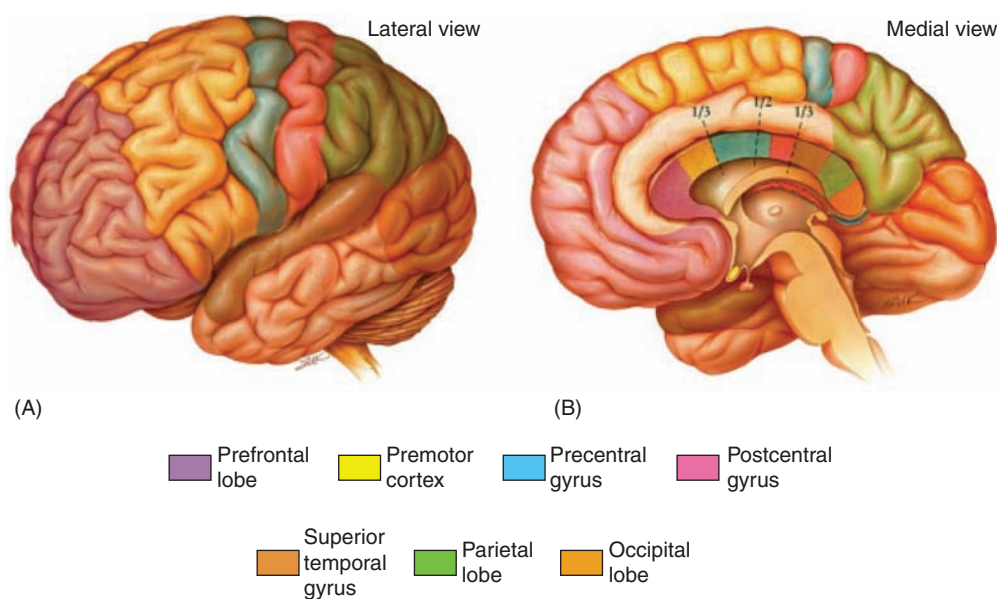
A severe form is the alien-hand syndrome, in which a patient's speaking left hemisphere cannot name or identify an object held in the left nondominant hand, but the patient can select the object under guidance from his right dominant hemisphere. In clinical practice, this is rarely seen; instead,

more complex neurological signs are more common: mutism, ataxia, alexia, hemineglect, gait apraxia, and urinary incontinence.

Neurological deficits depend on which fibers are disrupted at the site of the callosal lesion. Postmortem morphological studies have shown that connections of the corpus callosum are loosely organized in a rostral-caudal manner, with the frontal lobes occupying the rostral portion of the callosum and the parietal, temporal, and occipital lobes following in an anterior-posterior representation (Figure 31.9). Lesions at the isthmus of the corpus callosum, for instance, are likely to result in alien hand syndrome as information relayed to the precentral gyrus, a brain region involved in inhibitory control over involuntary motor responses, are disrupted (44). See Table 31.3 for a summary of disconnection syndromes.

### Corpus Callosotomy Versus Vagus Nerve Stimulation

The advent of vagus nerve stimulation (VNS) for the palliation of severe seizure disorders has put in question the indications for callosotomies. In one study, callosotomies were found to provide a slightly better control rate (79% vs. 50% reduction of seizures by 50% or more) and similar rates of control for atonic seizures. Yet complications of callosotomies were also higher, 21% versus 8% compared with VNS (39). An advantage of VNS is that it is associated with less immediate morbidity, given that it is less invasive than a callosotomy; but, some studies report lower overall permanent morbidity rates for callosotomies. Since VNS is less invasive, it is often tried first (39), although many still believe that the outcome would be better after a corpus callosotomy particularly in a patient with atonic drop attacks.



**FIGURE 31.9** Topography of cerebral cortex and associated commissural fibers.

Source: From Ref. (45). Jea A, Vachhrajani S, Widjaja E, et al. Corpus callosotomy in children and the disconnection syndromes: a review. *Childs Nerv Syst.* 2008;24(6):685–692.

**TABLE 31.3 Summary Of Disconnection Syndromes and Associated Timing After Callosotomy, Site of Callosal Lesion, and Consequent Hemispheric Disconnection**

TIMING	DISCONNECTION SYNDROME	SITE OF HEMISPHERIC DISCONNECTION	SITE OF CALLOSAL LESION
Acute	SMA syndrome	Premotor cortex	Unknown
Chronic	Alien hand syndrome	Precentral gyrus	Posterior 1/2
	Dichotic listening suppression	Superior temporal gyrus	Isthmus
	Tactile dysnomia	Postcentral gyrus	Unknown
	Hemispatial neglect	Postcentral gyrus	Unknown
	Nondominant hand agraphia	Parieto-occipital lobe	Splenium
	Alexia without agraphia	Parieto-occipital lobe	Splenium
	Tachistoscopic visual suppression	Occipital lobe	Splenium

### Hemispherectomy

A hemispherectomy involves the removal or disconnection of one cerebral hemisphere. Hemispherectomies are indicated for medically refractory patients whose seizures arise from diffuse regions of a single hemisphere or for patients with severe or progressive unilateral cortical disease.

Surgical candidates are those with profound contralateral neurologic deficits in which resecting less than a hemisphere would be inadequate. Most epilepsy centers employ a set of criteria for this procedure. Patients who undergo a hemispherectomy often have one of the following:

1. *Hemimegalencephaly*, a malformation of cortical development involving the proliferation of neuronal and glial cells in one cerebral hemisphere
2. *Infantile-type hemiplegia and seizures*, such as from Sturge-Weber syndrome that involves unilateral intracranial angiomas
3. *Rasmussen's encephalitis*, a T-lymphocyte inflammatory condition localized to one hemisphere
4. *Hemispheric stroke*, usually occurring in the perinatal period.

Hemispherectomies waned in the 1960s after reported obstructive hydrocephalus, superficial hemosiderosis, and intracranial hematomas in as many as 33% patients (46). Many complications still exist today, but the surgery has been continuously modified to minimize them, and the procedure continues to be considered in certain cases due to excellent seizure-free outcomes.

### Surgical Techniques

There are two main types of hemispherectomies: the classical anatomic hemispherectomy and the functional hemispherectomy. Functional hemispherectomies have paved the way to hemispherotomies, which will also be discussed (Figure 31.10). The evolution of operations has resulted in the preservation of more subarachnoid space, required smaller craniotomies, and taken less operative time. Outcomes between

these surgeries remain comparable, though literature shows that hemispherotomy techniques could be better suited in children with perinatal stroke, Rasmussen encephalitis, and Sturge-Weber syndrome (47), whereas a modified functional or anatomic technique could be better suited in patients with hemimegalencephaly and cortical dysplasia (48–50).

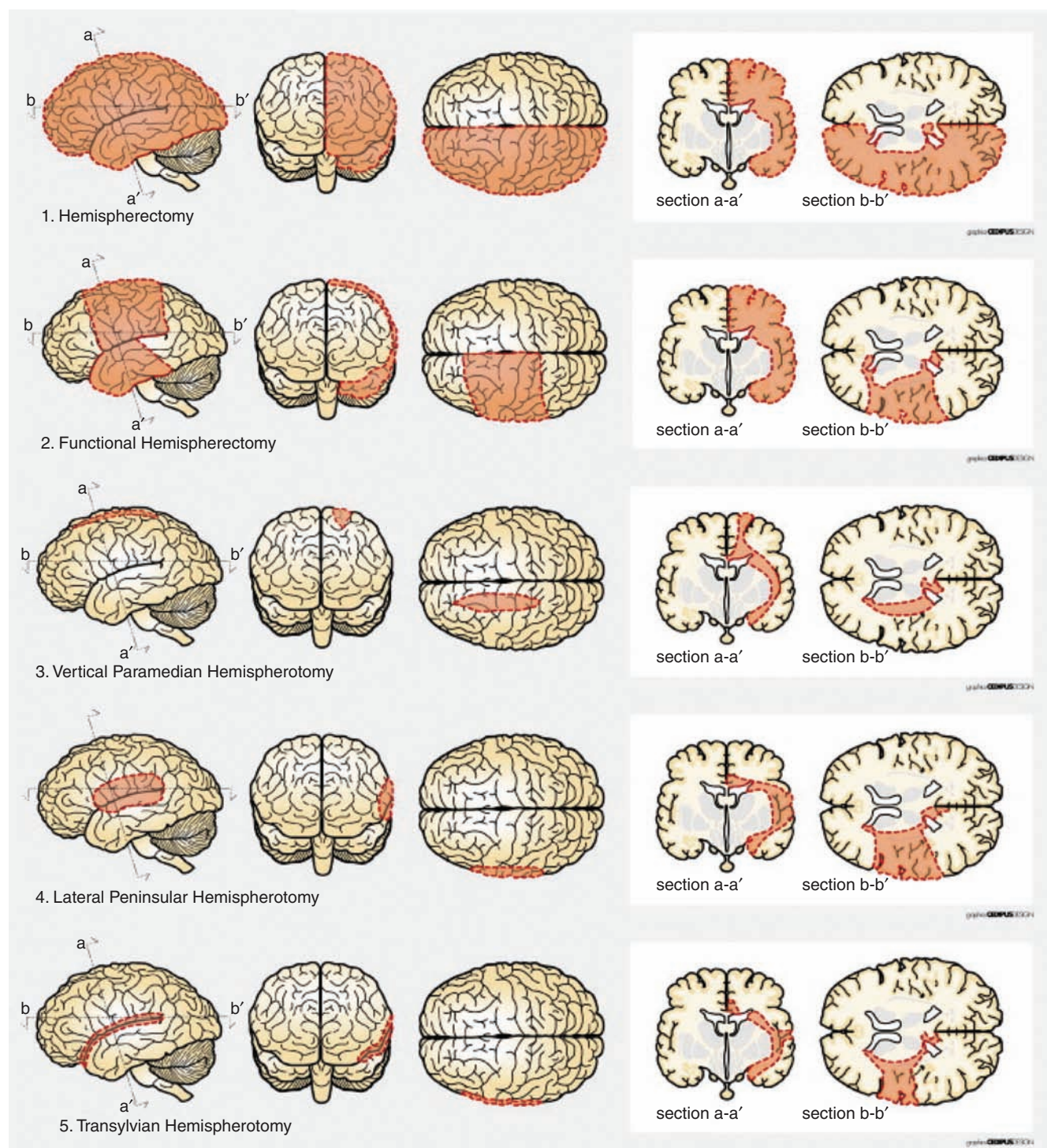
*Anatomic Hemispherectomy.* Anatomic hemispherectomy involves the complete removal of an entire hemisphere, making it the most radical form of epilepsy surgery. Resection occurs in a piece-wise fashion, sparing the basal ganglia after ligation of the major vessels. Despite how radical it is, this procedure is still being performed at some epilepsy centers because it has the advantage of ensuring a complete disconnection.

Briefly, the surgeon enters the middle temporal gyrus and carries a dissection to the temporal horn of the ventricle, approximately 2 cm deep to the gray–white junction, and posteriorly in a C-shaped fashion around the sylvian fissure. Branches of the MCA are coagulated. A C-shaped trough from the temporal lobe, behind the sylvian fissure and along the inferior frontal lobe, is created and then the temporal and frontal lobes are simultaneously removed. A standard anterior lobectomy is performed except that the entire superior gyrus is removed from the most proximal portion of sylvian fissure posteriorly until the trough is encountered. The vein of Labbé is spared and the distal MCA is coagulated. An amygdalohippocampectomy is then performed. Then a frontal lobe resection is conducted, starting at the motor strip around the sylvian fissure and progressing medially toward the sagittal sinus. Dissection continues anteriorly in the superior frontal gyrus until the orbital ridge is encountered. The superior frontal gyrus is then retracted laterally off the falx. The ipsilateral ACA is clipped, and the parietal lobe is removed, starting laterally at the level of the trough, around the Sylvian fissure and posteromedially in the parietal gyrus. Dissection continues anteriorly parallel to the sagittal sinus. After the splenium is identified, the parietal lobe is resected completely. A subpial removal of the cingulate gyrus follows. The last lobe that is removed is the occipital lobe.

**Functional Hemispherectomy.** Functional hemispherectomy was introduced after observations that subtotal hemispheric resection led to fewer postoperative complications, albeit worse seizure control. A functional hemispherectomy consists of subtotal hemispheric removal, but complete disconnection.

The goal is to achieve seizure control comparable to anatomical hemispherectomy, but with lower complications.

The surgeon excises the temporal lobe, including the amygdala and hippocampus. He then excises the frontoparietal region down to the corpus callosum, where



**FIGURE 31.10** Hemispherectomy v. functional hemispherectomy v. hemispherotomies.

Source: From Ref. (51). Marras CE, Granata T, Franzini A, et al. Hemispherotomy and functional hemispherectomy: Indications and outcome. *Epilepsy Res.* 2010;89(1):104–112.



the frontal and parietooccipital fibers entering the corpus callosum are disrupted. The insular cortex is removed.

*Hemispherotomy.* The success with functional hemispherectomy led to modifications involving smaller cortical removal allowing disconnection of the remaining tissue. This final evolution is known as a hemispherotomy. In a peri-insular hemispherotomy, there are three main surgical stages: the supra-insular window, the infra-insular window, and the insula resection or disconnection. The goal of the *supra-insular window* stage is to enable disconnection of the suprasylvian portion of the hemisphere and gain access to the ventricle to reach the corpus callosum. The *infra-insular window* stage allows for the disconnection of the temporal lobe, after which the *insular resection* can be performed while preserving arteries and veins. Following these three stages, the whole hemisphere is disconnected and kept vascularized.

#### *Surgical Timing*

The timing of a hemispherectomy is often debated. If untreated, epileptiform discharges gradually damage the contralateral hemisphere, resulting in severe intellectual impairment. Studies show that early surgical intervention results in improved psychosocial and intellectual benefits. These results point to surgical interventions at the beginning of seizure onset, even before maximal hemiparesis in the case of Rasmussen's syndrome. To prevent inevitable intellectual deterioration, surgery is encouraged on patients even when the motor deficits are mild and even if the patient would be left with worse deficits postoperatively (14).

#### *Complications*

Anatomic hemispherectomies are associated with early severe complication rates of 6.6% to 10% and late mortality rates of up to 30%. Complications include hemorrhaging into the large resection cavity. This problem can be compounded by sensorineural hearing loss as iron levels from blood-breakdown in the spinal fluid damage the eighth cranial nerve (52–55).

The overall general hemispherectomy mortality rate is 1% to 3%, and is usually a consequence of other perioperative complications (14). Complications range from fever, hypotonia, aseptic meningitis to brainstem trauma, gross edema of the contralateral hemisphere, superior sagittal sinus occlusion, and hydrocephalus. Other complications include motor dysfunction, visual field cuts, paretic gait, helper hand, and disconnection syndromes.

#### *Outcomes*

Sixty to 94% of patients experience complete or near-complete seizure freedom (56). In a series on children with Rasmussen's encephalitis, 89% of patients achieved complete

or near-complete seizure freedom (56). Outcomes for Sturge-Weber syndrome and perinatal stroke patients are similarly good with 73% to 93% patients achieving seizure freedom.

The outcomes for hemimegalencephaly are worse, in terms of both operative complications and seizures (57,58). Reported rates of seizure-freedom for hemimegalencephaly and cortical dysplasia patients are 63% to 80% (47,59,60).

In terms of intellectual impairment, generally the greater the intellectual capacity of the patient prior to surgery the greater the decline in function. Most patients have mild to severe mental retardation post surgery, but this is usually already present beforehand.

### **Multiple Subpial Transection**

MST is indicated for patients with an epileptogenic focus in eloquent cortex thought to be inoperable, such as pre- and postcentral gyrus, Broca's area, and Wernicke's area. Transections disrupt the horizontal cortical connection and conduction of electrical activity, which is essential for the development of synchronous discharge and seizures. However, the vertical columnar arrangement of the cortex remains intact, preserving function. A small transector is used to place small cuts perpendicular to the pial surface, 5 mm apart from each other.

### **GENERAL RISKS OF EPILEPSY SURGERY**

The removal of essential areas of cortex coupled with injury of projection fibers, association fibers, or commissural fibers can lead to deficits. The most common deficit after temporal lobectomy is a contralateral (homonymous) superior quadrantanopsia ("pie in the sky" defect) due to injury to Meyer's loop. Other potential complications include hemorrhage, infarction (commonly of deep penetrating vessels leading to lacunar stroke), infection, incomplete resection, memory impairment, transient dysnomia, and mood changes.

### **OUTCOME CLASSIFICATION**

There is variation reflecting institutional and experts' opinions on how to best report outcomes for epilepsy surgery.

The Duke System for classifying postoperative outcomes for epilepsy surgery uses a rating from Class 1 to Class 3:

Class 1: Seizure free or auras

Class 2: <10 seizures/year

Class 3: >10 seizures/year.

However, the Engel classification has become the *de facto* postsurgical assessment tool in medical literature. It is important to state that the outcomes do not specify the need for continued medication following surgery. The Engel classification, which was introduced in 1987, uses a rating from Class I to Class IV:



- Class I: Free of disabling seizures (completely seizure free; nondisabling, simple partial seizures only; some disabling seizures, but free of disabling seizures for at least 2 years; generalized convulsion with antiepileptic drug withdrawal only)
- Class II: Rare disabling seizures (initially free of disabling seizures, but rare seizures now; rare disabling seizures since surgery; more than rare disabling seizures, but rare seizures for at least 2 years; nocturnal seizures only)
- Class III: Worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 years)
- Class IV: No worthwhile improvement; some reduction, no reduction, or worsening is possible (61)

Recently, the International League Against Epilepsy (ILAE) introduced its own instrument. In this system, surgical outcome is rated on a scale from Class 1 to Class 6. This system is meant to reflect a change in classification over successive years and address problems with the Engel system such as ambiguity of the meaning of “worthwhile improvement,” problems in dealing with outcomes of patients whose seizures tend to cluster together, and the inability to compare results with drug trials:

- Class 1: Completely seizure free; no auras
- Class 1a: Completely seizure free *since surgery*; no auras
- Class 2: Only aura, no other seizures
- Class 3: One to three seizure days per year; may have auras
- Class 4: Four seizure days per year or up to 50% reduction in seizure days from baseline; may have auras
- Class 5: Less than 50% reduction in number of seizure days from baseline, or an increase in seizure days of up to 100% from baseline
- Class 6: Increase in number of seizure days from baseline of more than 100% (62)

### Difficulties With Outcome Studies

There are few Class I evidence studies for epilepsy surgery. This is due to the difficulties involved in designing and implementing the studies. Given that uncontrolled epileptic seizures may increase the risk of death fivefold (63), it becomes ethically challenging to design a study that randomly assigns patients to surgery versus pharmacotherapy arms. The fact that most epilepsy centers report seizure-free rates of 70% to 90% postsurgery further exacerbates these ethical complexities (64).

It was not until 2001 that a randomized, controlled trial, which is viewed as the gold standard for the evaluation of

therapeutic efficacy, was finally conducted for epilepsy surgery. The study was justified ethically because the waiting list for surgery at the institution of the study exceeded one year (65). The study found that 58% of patients randomized to be evaluated for surgical therapy were free of disabling seizures, compared with 8% free of disabling seizures in the group randomized to continued medical therapy ( $P < .001$ ). The study also found surgery to be superior to medical therapy in terms of quality of life, rates of employment, and school attendance at one year (65). To date, there have been no other completed randomized control trials studies for temporal lobectomy or for other epilepsy surgeries. Most information on epilepsy surgery outcome is based on retrospective Class IV evidence.

In 2003, the American Epilepsy Society and the American Association of Neurological Surgeons used the results of the 2001 Class I evidence study in addition to those of 24 Class IV evidence studies to emphasize the recommendation that patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs be considered for referral to an epilepsy surgery center. They also recommended that patients who meet the criteria for antero-mesial temporal lobe resection and accept the risks and benefits of this procedure should be offered surgical treatment. At the time there was not enough evidence to make definitive recommendations on the role of surgery in neocortical epilepsy (66).

Since epilepsy surgery centers perform few multilobar resections, hemispherectomies, corpus callosotomies, lesionectomies, and multiple subpial transections compared to anteromesial temporal lobe and localized neocortical resections, there are less objective data concerning surgical outcomes, including risks and benefits analyses, in these procedures.

### Long-Term Outcome Studies

A 2013 population-based, prospective study from Sweden has shown good long-term seizure outcomes after resective epilepsy surgery. In the study, the majority of the patients who are seizure-free after 5 to 10 years have sustained seizure freedom since surgery (67). Specifically, in the long term (mean 7.6 years), 62% of operated adults and 50% of operated children were seizure-free, compared to 14% of nonoperated adults ( $P < .001$ ) and 38% of nonoperated children (67). Other studies have shown similar numbers (68). Many of the patients who attain seizure freedom are able to successfully discontinue AEDs, though interestingly in most cases this has been children.

It has been suggested that benefits gained from surgery decrease in efficacy over time. In fact, the probability of seizure freedom has been estimated as 75% (95% confidence interval [CI] 70–80%), 67% (62%–72%), and 51% (45%–57%) at 2, 5, and 10 years' follow up, respectively (68). Approximately 50% of seizure recurrences tend to occur within the first two postoperative years (68). Relapse is less likely to occur the longer an individual is seizure-free, and remission is less likely to occur the longer seizures continue (69). Experience across institutions has shown that patients who

have had extratemporal resections are more likely to have seizure recurrence in the long term than those who had anterior temporal resections. Definitive long-term prognostic factors are difficult to define since epilepsy surgery outcome studies are complicated by patients with a mix of lesional cases, various types of epilepsy, various management strategies, multiple surgeons, etc. Factors thought to predict favorable outcomes include unifocal lesion on MRI, unilobular resection, complete resection, an active region on EEG, and absence of preoperative generalized tonic-clonic seizures.

### Outcome Studies in Children

Epilepsy management in children can differ from that in adults. This is partly due to the developmental state of the brain of children and the fact that syndromes in children are more different and more heterogeneous than in adults. For instance, cortical dysplasias and tumors are the most common syndromes, followed by neurocutaneous disorders and hemispheric syndromes (Rasmussen's encephalitis, hemimegalencephaly).

In general, children are more likely than adults to undergo a repeat surgery with 6% to 21% likely having a second operation (70). This is in large part due to the prevalence of cortical dysplasia in children and a greater likelihood of incomplete resection following this type of surgery. Of those who undergo a repeat surgery, 30% to 70% will be seizure free (70).

Despite everything, the overall rates of seizure freedom after surgery are comparable in both children and adults, and range from 58% to 78% (70). Rates of postneocortical resection seizure freedom are also comparable, with overall freedom from seizures in 59% to 70% of children (60%–91% for temporal and 54%–66% for extratemporal resections) (70). Other outcomes of epilepsy surgery, however, may be different. Milder lasting impairments can be anticipated in children than in adults, given the developing brain's plasticity; but higher perioperative complications are also expected given smaller total blood volumes. Indeed, mortality related to surgery in children, including early postoperative deaths (secondary to infections, hydrocephalus, dehydration, hemorrhage) and late postoperative deaths (unexplained or related to seizures), is estimated at 0%–2%, which is higher than in adults (70).

Factors predicting favorable outcomes in pediatric epilepsy include unifocal lesion on MRI, unilobular resection, complete resection, an active region on EEG, and absence of preoperative generalized tonic-clonic seizures. These factors are similarly used to predict a favorable outcome in adults.

Epilepsy surgery is a viable treatment option for patients whose seizures have remained intractable despite AED use. Despite epilepsy surgery having been available for many decades, only a small percentage of patients who are potentially eligible for surgery are referred to epilepsy surgery centers. The surgical evaluation process is detailed and can involve many steps, including vEEG monitoring,

sophisticated imaging, and other tests. Depending on the site of seizures and the underlying pathology, many different types of surgeries are possible. Many surgeries offer a greater than 50% chance of long-term seizure freedom.

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# Dietary Therapy

*Candace Richardson and William B. Gallentine*

The classic Ketogenic diet (KD) is a high-fat, low-carbohydrate treatment that has been used in the treatment of epilepsy for nearly 100 years. When implemented correctly, KD therapy induces a state of ketosis by making dietary fat the main source of energy for the body. This state of ketosis mimics fasting, which has long been associated with beneficial effects in epileptic seizures. In the past 20 years there has been a renewed use of diet treatment for epilepsy and development of modifications, which allow more protein and carbohydrate intake and require less fat intake. The newer diet treatments do not always produce the levels of ketosis found in patients on the classic KD, but do maintain a steady blood glucose level, avoiding postmeal glucose rises seen with a typical diet. Despite continued advancements in the development of antiepileptic drugs (AEDs), approximately 30% of patients with epilepsy have refractory seizures, representing a significant need for additional treatment options. Because of this need, the use of metabolism-modifying diets remains a therapeutic option for drug-resistant epilepsy. After careful screening and education, metabolic treatment can be used in children or adults to provide a safe, well-tolerated therapy for many forms of epilepsy. This chapter will discuss some practical aspects of implementing metabolic treatment for epilepsy.

## HISTORY

Fasting and other diet-based therapeutic approaches have long been used to treat epilepsy. Fasting is, in fact, the only therapeutic measure for epilepsy recorded in the Hippocratic collection. The origin of modern KD therapy came in 1921, when Dr. Rawle Geyelin gave a presentation at the annual meeting of the American Medical Association in which he reported the outcomes of several children with epilepsy who had benefited from fasting under the care of osteopathic physician Dr. Hugh Conklin. For some of those children the reduction in seizures was long lasting. That same year, the Mayo Clinic Bulletin published the first description of a “ketogenic diet.” In this description, dietary intake was calculated to simulate ketosis, a metabolic state that develops during fasting. This was accomplished by restricting

protein and carbohydrate intake and supplying dietary fat as a source of calories, thereby mimicking the body’s use of its own fat during a fasting situation. For the 20 years that followed, primarily because of researchers at the Mayo Clinic, the KD became a popular and well-studied treatment for both children and adults with epilepsy. However, as AEDs were introduced into the United States, use of the KD declined until it was used only at a few academic centers.

The medium-chain triglyceride (MCT) oil diet was developed about 40 years ago to provide a diet approach that produced a similar level of ketosis as the classic KD while allowing for more carbohydrate. In the past 20 years, the Modified Atkins diet (MAD) and Low Glycemic Index Treatment (LGIT) have been developed, which have shown that the fat content of the treatment does not have to be as high as traditionally believed.

Metabolic treatment is currently being used all over the world, and there is a growing scientific interest in the physiological basis of the diets’ beneficial effects. At this writing, a PubMed search revealed that since 1994 over 1,100 peer-reviewed articles have been published on the KD. Randomized, controlled trials and meta-analyses consistently show that about 50% of children respond (ie, at least a 50% reduction in seizures) to this metabolic therapy. There are also indications that metabolic treatment may be effective for adults with epilepsy and in status epilepticus (SE), and it is a first-line treatment of seizures associated with glucose transporter-1 (GLUT-1) deficiency. Given that approximately 200 centers offer this treatment today, it is estimated that about 3000 children may be actively receiving metabolic treatment (1). With the growing use and awareness of metabolic treatment for epilepsy, an expert committee of 26 neurologists and dietitians from 9 countries has recently published a consensus guideline endorsed by the Child Neurology Society. This guideline offers recommendations for optimal management of children on the KD, and it offers clarification on certain aspects of KD implementation that have often diminished efficacy or caused complications in situations where clinicians have not been trained in appropriate diet management (2). The current guideline helps inform decisions on patient selection,



pre-KD counseling and evaluation, specific dietary therapy selection, implementation, supplementation, follow-up management, adverse event monitoring, and eventual KD discontinuation.

### PHYSIOLOGICAL BASIS FOR THERAPEUTIC EFFECTS

The mechanism of action of the KD in seizure control is not known. Importantly, however, all variants of the KD share the common characteristic of restricting carbohydrate intake and making fat the primary source of energy for the brain. The resulting metabolic state somehow affects neuronal excitability, and thus far the unknown mechanism appears to be unique from the mechanisms of action of other anticonvulsant therapies. Restriction of carbohydrate is clearly critical; it has been reported that children whose seizures were well controlled on KD therapy experienced a recurrence of seizures within 1 hour of intravenous infusion of glucose (3). Emerging data indicate that the beneficial effects of KDs on epilepsy may arise from a variety of different mechanisms that include carbohydrate reduction, activation of ATP-sensitive potassium channels by mitochondrial metabolism, inhibition of the mammalian target of rapamycin pathway, and inhibition of glutamatergic excitatory synaptic transmission. The importance of mitochondria to energy homeostasis makes them an important point of focus in current research on the mechanism of action of metabolic treatment.

### EFFICACY

Since the renewal of interest in the KD, hundreds of case reports and prospective studies have yielded very similar results. Approximately 50% to 60% of children experience seizure reduction of at least 50%, and about one-third of children see their seizures reduced by greater than 90% (4). About 10% of children become seizure-free after using the KD, and there is no apparent variation with sex or age of the children (2). Moreover, the response seems to be quite durable, with many children maintaining seizure control over a period of years. In some cases, seizure control even continues after the KD has been stopped. It is also important to note that a randomized controlled trial has published results that were very representative of the overall trends that were drawn from the case reports and prospective studies mentioned earlier (5). In this trial, 103 children who experienced daily seizures despite treatment with at least two AEDs were randomized to the KD or to a control group. After 3 months, 38% of the children in the KD group had greater than 50% seizure reduction, compared to 6% of the control group ( $P < .0001$ ). Seven percent of the KD group had greater than 90% seizure reduction compared to 0% of the control group ( $P = .0582$ ). There was no indication of a significant difference in the efficacy of the KD between symptomatic generalized or symptomatic focal syndromes.

### Efficacy in Subpopulations: Infantile Spasms

Results from a study of 104 children (mean age 1.2 years) indicate that intractable epilepsy due to infantile spasm (IS) responds very well to KD and suggest the diet may come to be considered as a first-line therapy for IS (6). The children in this study had already been treated with an average of 3.6 AEDs; 71% included corticosteroid or vigabatrin. Using an intent-to-treat analysis, greater than 50% improvement occurred in 64% of the children after 6 months of treatment, and 77% responded after 1 to 2 years. Furthermore, 37% of the children became spasm-free for at least a 6-month period within 2.4 months (median) of starting the KD. Notably, 62% showed improvement in development, 35% had EEG improvement.

### Efficacy in Subpopulations: Adults

At present, there are few reports on the use of KD in adult epilepsy, but the available data suggest that the KD successfully reduces seizures in adults (4). Unfortunately, the KD can be challenging to use in adults due to the necessity of making very restrictive lifestyle changes in order to achieve and maintain a therapeutic level of ketosis. However, a MAD has recently shown efficacy in a study of 30 adults (aged 18–53 years) with intractable epilepsy (7). Using an intent-to-treat analysis, 47% of the participants experienced more than 50% seizure reduction after 1 month and 3 months on the MAD. The median time to improvement was 2 weeks (range: 1–8 weeks). After 6 months on the MAD, 33% had greater than 50% seizure reduction; unfortunately, 30% of the participants discontinued the MAD before 3 months. Limited data indicate that long-term use of the Atkins diet in adults with obesity is safe. This observation suggests that use of the MAD for seizure control may be considered for motivated adults.

### Efficacy in Subpopulations: Febrile Infection-Related Epilepsy Syndrome

There is mounting evidence appearing in the literature that the KD is effective in cases of febrile infection-related epilepsy syndrome (FIRES), which can be quite difficult to control and can adversely affect development (4). There has been a report on nine children with FIRES who presented in SE that was refractory to conventional treatment (8). The KD was given to these children as a ketogenic formula administered via tube feeding; in seven patients seizures stopped within 2 to 4 days (mean 2 days) after the onset of ketonuria and 4 to 6 days (mean 4.8 days) following the onset of the diet. The patients recovered consciousness within 24 to 48 hours after the seizures had stopped, and they recovered motor function within the following weeks. Six of the responders remained on the KD for 6 months to 2 years (mean 1 year). Within a few months seizures recurred, but they consisted of isolated seizures occurring once or twice a week.

## CLINICAL IMPLEMENTATION

### Overview

Successfully implementing and maintaining treatment depends on close collaboration of the metabolic team with the patient and family. A skilled dietitian on the team is essential to maintain appropriate dietary and calorie intake. Dietitian support throughout therapy is important to success because small changes in diet composition can correct or prevent issues like weight loss, growth failure, or discontinuation due to prescribed foods becoming boring or unpalatable. In addition to the dietitian, the team typically includes a pediatric neurologist, epilepsy nurse, and pharmacist, all who have knowledge of, and experience with, metabolic treatment. Therapy is usually recommended for at least a 3-month trial. After a patient has completed initiation of the metabolic treatment, fine-tuning may be needed to maximize the diets' efficacy, ensure good tolerability, detect and minimize complications, and meet changing nutritional requirements to compensate for growth in children. If seizure activity is reduced, the treatment can, in some cases, be weaned in about 2 years. In some patients, weaning may become possible earlier; others may continue on the therapy for many years.

### Treatment Options

All variations of metabolic treatment involve specific adjustments in the proportion of total calories from fat, protein, and carbohydrate, which will lead to the lower glucose levels and/or state of ketosis that has been observed in patients successfully treated with diet therapy. The proportion of ketogenic foods (high in fat) to nonketogenic foods (high in carbohydrates and/or protein) is referred to as the diet ratio as seen in Table 32.1. In sharp contrast to the diet ratios seen in the treatment diets, a typical American meal provides about 50% of the calories from carbohydrate, 30% from fat, and 20% from protein. Higher diet ratios correspond to a higher percentage of calories from fat as can be seen in Figure 32.1. The forms of metabolic treatment also vary in their implementation with some requiring carefully weighing foods on a gram scale according to calculated meal plans

or in contrast using household measures for food portions and counting grams of carbohydrate and possibly protein and fat to adhere to recommended intake goals. Clearly, effective implementation of this therapy involves significant lifestyle changes and commitment on the part of the patient and family. Therefore, in many cases, the patient or family is involved in the decision regarding the form of metabolic treatment.

For some children, it is important that the diet plan maintains elevated levels of blood ketones. Another important goal is to avoid increases in blood glucose levels after carbohydrate consumption. Figure 32.2 illustrates the respective compositions, or ratios, of different metabolic options currently being used in epilepsy treatment.

- The “classic” KD has been used to treat epilepsy since the 1920s. The classic KD is typically 3 to 4 grams of fat (ketogenic) for every 1 gram of protein plus carbohydrate (nonketogenic).
- The MCT diet incorporates MCT oil as a contributor to the total fat intake in the diet. Since medium-chain triglycerides are more ketogenic than other fatty acids, this addition lowers the total amount of fat needed and allows children to eat more protein and carbohydrate with this diet than with the classic KD.
- The LGIT allows for more carbohydrates than the other three diets. However, all the high carbohydrate foods the child eats must have a low glycemic index. The glycemic index is a measure of how much a particular food raises postprandial blood glucose.
- The MAD, as the name suggests, is a modification of the Atkins diet used for weight loss. When starting the diet, children are allowed about 10 grams while adults are allowed about 20 grams of carbohydrate per day, and they get about 60% of their calories from fat.

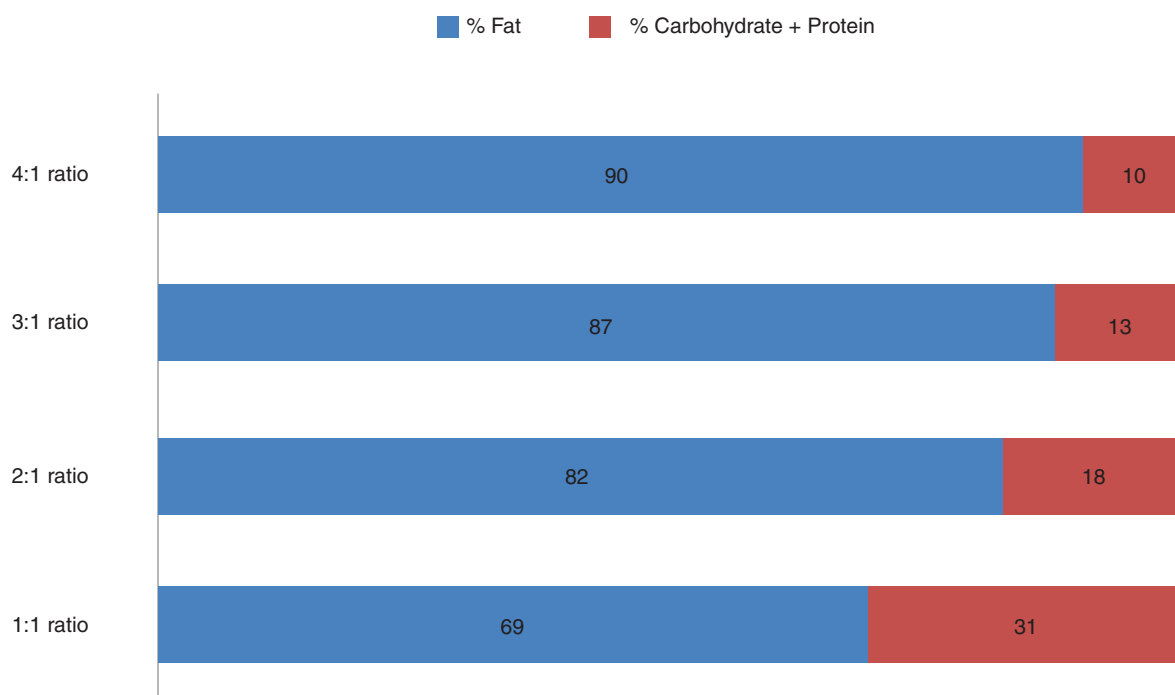
Meals, on all treatment options, will include a source of fat such as butter, oil, mayonnaise, or cream. In addition, meals include meat, egg, or cheese as the protein source. The carbohydrate allotment will typically be a small serving of fruit or vegetable. Since fat provides 9 kcal per gram compared to 4 kcal per gram from carbohydrate and protein, a high-fat diet will include smaller portions of foods as can be seen by comparing the 500-calorie ketogenic meal in Figure 32.3A and the more typical 500-calorie meal in Figure 32.3B.

A flexible approach may also be used to prescribing the treatment diet. The patient may begin treatment with one specific type of diet, but it is also possible for the ketogenic dietitian to combine features from some or all of the diets represented in the Figure 32.2. For example, MCT oil may be added to classic KD or MAD. Use of all metabolic treatments involved the same contraindications and they all require careful monitoring, fine-tuning, and consideration of micronutrient supplementation requirements. Choice of diet plan in some cases may be determined by patient age, dietary preferences, or feeding methods. A pretreatment diet assessment conducted by the ketogenic dietitian is instrumental

**TABLE 32.1 Understanding the Ketogenic Diet Ratio**

The ratio determines the proportion of calories from ketogenic foods (high % of calories from fat) and nonketogenic foods (high % of calories from protein and/or carbohydrate)

DIET RATIO	FAT GRAMS	PROTEIN AND CARBOHYDRATE GRAMS
1:1	1	1
2:1	2	1
3:1	3	1
4:1	4	1



**FIGURE 32.1** Relationship of ketogenic diet ratio to percentage of fat to nonfat calories.

in weighing the treatment options and determining the appropriate choice for each patient. Patient and family preference must also be strongly considered in the diet decision. Finally, it should be noted that a recent study of 40 patients with symptomatic intractable epilepsy made a comparison between the classic KD ( $n = 10$ ), the MAD ( $n = 15$ ), and a normal, unchanged diet ( $n = 15$ ) (9). They found that the frequency and severity of seizures showed the best improvement in the classic KD patients followed by the MAD group, then the patients on a normal, unchanged diet using AEDs only.

### Potential Candidates for Therapy

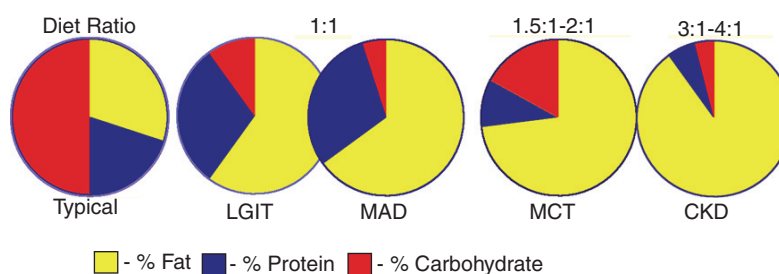
Metabolic treatment is an established, nonpharmacologic treatment for intractable seizures of various etiologies that is both safe and effective. Data suggest that patients with

seizures that are resistant to two AEDs should be considered for metabolic treatment given the diets' efficacy and the low probability of significant improvement with additional trials of AEDs. Table 32.2 lists indications for metabolic treatment based on the evidence that is presently available (4).

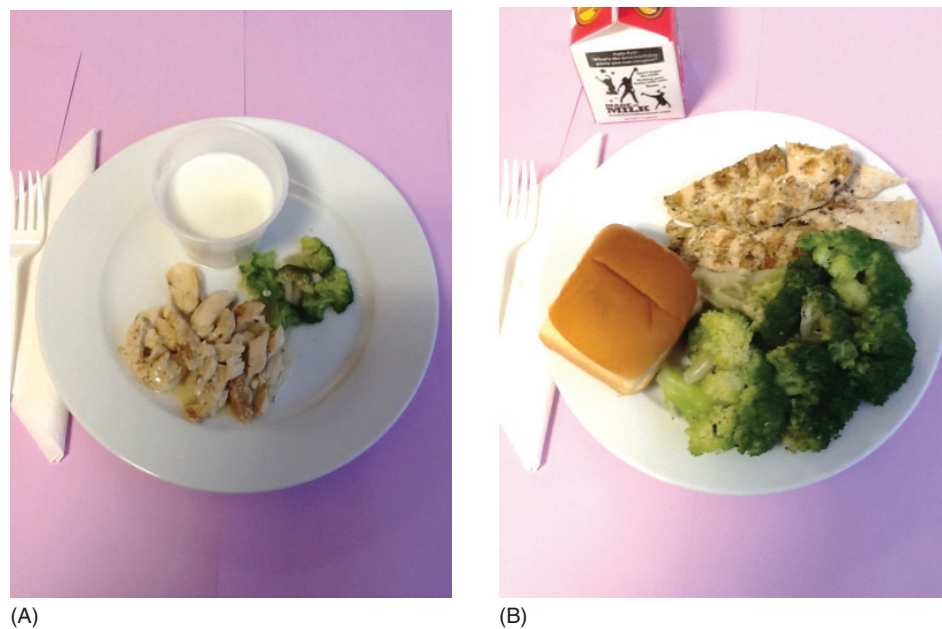
There is also support in the literature for using classic KD therapy in cases of Lennox-Gastaut syndrome (10), and very good response rates have been reported for children with absence epilepsy (11).

### Pathway to Initiation of Therapy

As indicated in Table 32.3, starting metabolic treatment requires extensive advance preparation. After a referral has been made to the ketogenic dietitian, actual initiation of the diet is preceded by a thorough nutrition assessment, including a 3-day food record, a review of medications to



**FIGURE 32.2** Comparison of diet ratios and treatment options.



**FIGURE 32.3** Comparison of ketogenic meal (A) to more typically meal (B). Both meals provide 500 calories.

Note: Food portions are small because of the high fat content in the diet. Both of these meals provide 500 calories. Ketogenic meal: 86 grams heavy cream (296 calories); 12 grams broccoli; 34 grams chicken; 20 grams butter. Nonketogenic meal: 240 grams 1% milk (101 calories); 180 grams broccoli; 140 grams chicken (5 grams butter; 25 grams of dinner roll).

**TABLE 32.2** KD Therapy for Seizure Control: Indications and Contraindications

<i>Probable benefit (at least two publications)</i>
Glucose transporter protein-1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic–astatic epilepsy (Doose syndrome)
Tuberous sclerosis
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Selected mitochondrial disorders
Children receiving only formula (infants or enteral feedings)
<i>Contraindications</i>
Pyruvate carboxylase deficiency
Porphyria
β-oxidation defects:
Medium-chain acyl dehydrogenase deficiency (MCAD)
Long-chain acyl dehydrogenase deficiency (LCAD)
Short-chain acyl dehydrogenase deficiency (SCAD)
Long-chain 3-hydroxyacyl -CoA deficiency
Medium-chain 3-hydroxyacyl -CoA deficiency
Primary carnitine deficiency
Inadequate ability to maintain nutrition or comply with the KD restrictions
Children with clear focal lesion potentially resectable*

\*Relative

Source: Adapted from Ref. (4). Kossoff EH, Wang H-S. Dietary therapies for epilepsy. *Biomed J.* 2013;36(1):2–8.

**TABLE 32.3** Metabolic Treatment Roadmap

1. Referral to ketogenic dietitian.
2. Complete baseline studies.
3. Review of medications for carbohydrate content.
4. Patient or caregiver completion of 3-day food record.
5. Nutrition assessment completed.
6. Determination of metabolic treatment prescription including decision on in-patient or out-patient initiation.
7. Provide patient and/or caregiver education on initiation and management of treatment.
8. Scheduling initiation.
9. Initiation.
10. Monitoring and fine tuning.
11. Discontinuation of treatment.

determine their carbohydrate content, and obtaining some key baseline laboratory values. A specific diet treatment plan is developed based on the child’s age, activity level, route of feeding, developmental level, and current nutrition status.

*Baseline Studies*

In addition to the laboratory studies to rule out metabolic disorders that would be a contraindication to use of a high-fat metabolic treatment, Table 32.4 lists some laboratory values



**TABLE 32.4 Laboratory Evaluation Prior to Initiating KD**

Serum amino acids
Serum ammonia
Serum acylcarnitine profile
Lactic acid
Urine organic acids
Complete blood counts with platelets
Electrolytes including serum bicarbonate, calcium, zinc, selenium, magnesium, phosphorus
Serum liver and kidney tests
Fasting lipid profile
Urinalysis
Urine calcium and creatinine
Antiepileptic drug levels (if applicable)

that should be assessed before starting the metabolic treatment; these include, but are not limited to, serum glucose, albumin, total protein, fasting cholesterol and triglycerides, and serum chemistries. Also, since metabolic treatment has been associated with an increased chance of kidney stones, it is prudent to find out whether there is a strong personal or family history of kidney stones; a renal ultrasound and nephrology consultation may be needed.

#### **Review Carbohydrate Content of Medications**

The strictly controlled dietary intake of metabolic treatment leaves little room for the additional carbohydrates that may be found in medications. An upper limit of one gram of carbohydrate per day from medications and dietary supplements has been used by the authors. Patients who have responded well to metabolic treatment, but then exceed their daily carbohydrate limit, risk having a relapse of seizure activity. After excess carbohydrate intake it can take 2 to 3 days for metabolism to return to the preexposure state. Table 32.5 provides some examples of how medications may

**TABLE 32.5 Examples of Carbohydrate Content of Medications**

MEDICATION	CARB CONTENT (MG)
Amoxil Suspension 250 mg/5 ml – GSK	1855
Amoxil Suspension 400 mg/5 ml – GSK	1877
Amoxil Capsule 500 mg – GSK	0
Dilantin Suspension 125 mg/5 ml – Pfizer	297
Dilantin Infatabs 50mg (phenytoin) – Pfizer	473
Keppra 250 mg Tablet – UCB	0
Keppra Oral Solution 100 mg/ml – UCB	400
Lyrica 25 mg Capsule – Pfizer	75
Lyrica 50 mg Capsule – Pfizer	150
Lyrica 75 mg Capsule – Pfizer	25

contain amounts of carbohydrate that are quite significant when considered in the context of a diet that calculates daily carbohydrate intake down to the milligram. It is important to note that metabolic treatment is often initiated after the patient has failed two or three anticonvulsants, and is therefore likely to be initiated while the patient is on multiple medications. Pharmacists can serve an important role in helping minimize medications that have high carbohydrate content and avoid this error in the management of therapeutic ketosis.

#### **Nutrition Assessment**

Conscientious adherence to the diet plan greatly enhances the likelihood of successful seizure control. As illustrated in Table 32.6, it is essential for the ketogenic dietitian and the family to meet before the diet prescription can be determined and review a number of factors about the child. Any food allergies, food intolerances, or cultural/religious preferences need to be considered.

It is also important to identify any behavioral or personality traits that may significantly challenge consistent adherence to the meal plan. Finally, children with severe neurological impairments may require a swallow evaluation to ensure consistent nutrition and fluids. Patients can receive metabolic treatment through oral, tube, or parenteral intake of macronutrients; many patients receive both oral diet and formula through a feeding tube.

#### **Metabolic Treatment Prescription**

After the nutrition assessment is completed, the individualized therapeutic nutrition prescription for the metabolic treatment can be calculated. Table 32.7 lists the factors that the ketogenic dietitian considers when determining the appropriate fat: nonfat ratio to optimize the patient's chance of achieving a therapeutic level of ketosis. The complete nutrition prescription will specify calories, protein, fluid, vitamin and mineral supplements, number of meals and snacks or enteral feeding regimen and diet ratio or macronutrient gram goals, and amount of MCT oil (when

**TABLE 32.6 Preinitiation Nutrition Assessment Includes**

1. Review of medical history including GI problems and food allergies.
2. Anthropometric measurements and recent growth or weight change.
3. Food preferences or intolerances.
4. Feeding ability, swallowing difficulties, food liquid consistencies.
5. Functional level and physical activity level.
6. 3-day Food Record analysis for dietary intake, meal pattern, or feeding regimen and dietary supplements and fluid intake.
7. Review of laboratory evaluation.

**TABLE 32.7 Considerations in Prescribing Diet Ratio**

Age
Energy and protein requirements
Weight status and review of recent growth
Feeding route—oral, enteral, or combination
Functional level
Physical activity level
Patient or family preference

incorporated). Table 32.8 provides general age-based guidance on prescribing diet ratios.

Patients who will be initiated on treatment at a diet ratio of 1:1 are given the option of using household or gram measurements of foods. If household measures are used, patients are provided with guidelines for daily intake goals for grams of fat, carbohydrate, and protein that they will use to calculate the treatment diet. If weighing of foods will be used, then a set of calculated meal plans that provides gram weights of foods is calculated by the dietitian.

Meal plans are calculated from a ratio of grams of fat to grams of protein plus carbohydrate. The most common ratio is 4 g fat to 1 g protein plus carbohydrate (described as “4:1”). This means that 90% of the patient’s energy intake comes from fat and 10% from protein and carbohydrate combined. As illustrated in Table 32.9, after selecting the goal diet ratio and determining the individual calorie needs of the child, the ketogenic dietitian determines the number of daily dietary units. The units are used to determine the grams of fat and grams of nonfat that will comprise the daily meal plans. KetoCalculator is an online program that aids in this painstaking process by calculating meal plans that display food portions in gram units (12).

As mentioned earlier, the carbohydrate content of many medications can be significant in patients using KD therapy. KetoCalculator can also be used to factor in carbohydrate content of medications and dietary supplements in order to ensure that daily carbohydrate intake remains less than 1,000 mg. Using this software, the ketogenic dietitian can calculate an individualized vitamin and mineral profile to prescribe dietary supplements within the limitations of the diet prescription. This particular use of KetoCalculator is important because ketogenic diets are inherently inadequate in terms of vitamin and mineral intake. Therefore, all patients are given supplement recommendations that

**TABLE 32.8 General Guide in Selecting Diet Ratio Based on Age**

AGE	DIET RATIO
≤18 months	3:1
19 months–12 years	1:1–4:1
≥12 years	1:1–3:1

**TABLE 32.9 Understanding Dietary Units**

DIET RATIO	FAT CALORIES	PROTEIN + CARBOHYDRATE CALORIES	DIETARY UNIT CALORIES
2:1	2 g × 9 kcal = 18	1 g × 4 kcal = 4	22
3:1	3 g × 9 kcal = 27	1 g × 4 kcal = 4	31
4:1	4g × 9 kcal + 36	1 g × 4 kcal = 4	40

are typically started just after initiation on KD therapy. The dietary supplements are calculated, using specific products of known carbohydrate content, to provide at least 75%, but less than the Tolerable Upper Limit, of the Dietary Reference Intake for age for vitamins and minerals. Patients with free carnitine levels less than 20 nmol/mL will also have a recommendation for carnitine supplementation. Prescription L-carnitine is typically prescribed, with dosing starting at about 25 mg/kg, and given in three to four divided daily doses to be taken with food or formula.

The actual prescription of KD therapy is illustrated in a practical example. Table 32.10 shows the formulation of an individualized diet prescription for a patient based on her estimated needs.

Meal plans are calculated based on food preferences, and typically a set of 10 meal plans is initially calculated. An example of a day’s intake of three meals and one snack at a 4:1 diet ratio can be seen in Table 32.11.

Alternatively, commercial ketogenic formulas can be used in infants or in patients who require liquid formula for bottle or tube feeding (Table 32.12).

### *Patient and Caregiver Education*

The ketogenic team provides extensive education to caregivers using explanations, demonstrations, hands-on practice, and a Ketogenic Diet-Metabolic Treatment Handbook. This is done to equip the patient and family for the demands of

**TABLE 32.10 Example Calculation of a Ketogenic Diet Treatment Prescription**

Ann is a 5-year-old weighing 20 kg who will be initiated on KD. After the nutrition assessment the dietitian determines that a diet ratio of 4:1 is appropriate and estimated requirements are as follows:

59 kcal/kg and 0.95 g protein/kg; 1,170 kcal and 19 g protein daily.

Dietary units 1,170 kcal ÷ 40 (4:1 diet ratio) = 29.25 dietary units

Fat 29.25 × 4 = 117 grams of fat daily

Carbohydrate 29.25 × 1 = 29.25 grams of protein + carbohydrate daily  
29.25 – 19 (g protein daily) = 10.25 g carbohydrate daily

**Prescription:** 117 g fat, 19 g protein, 10.25 g carbohydrate daily

**TABLE 32.11 Example Calculate Meal Plans for One Day for Ann, 5-year-old, on Oral Diet**

Provides: 1,170 kcal, 19 g protein at 4:1 diet ratio in 3 meals and 1 snack.

Breakfast	Bacon with fruit and cream	
	Cream	36 g
	Fruit	9 g
	Bacon	18 g
	Oil, Canola	16 g
Lunch	Pepperoni Pizza Rounds	
	Cream	40 g
	Tomato sauce	15 g
	Cheese	14 g
	Pepperoni	13 g
	Oil, Canola	14 g
Supper	Cream of chicken soup with broccoli	
	Cream	42 g
	Broccoli	17 g
	Chicken	17 g
	Butter	26 g
Snack	Jello with whipped cream	
	Cream	20 g
	Diet jello	38 g

home management of KD therapy. Conscientious adherence to the diet plan greatly enhances the likelihood of successful seizure control. Education topics include:

1. Intake management including use of calculated meal plans or prescribed macronutrient gram goals, fluid intake goal and options, and prescribed dietary supplements.
2. Managing nondietary sources of carbohydrate, including personal care products and medications.
3. Home monitoring: monitoring log, weight checks, urine ketones, blood glucose, and blood ketones.
4. Managing special circumstances such as hypoglycemia or excess ketosis (Table 32.13).

**TABLE 32.12 Enteral Formula Options**

Ketocal® 3:1 powder
Ketocal® 4:1 powder
Ketocal® 4:1 liquid, flavored
Ketocal® 4:1 liquid, unflavored
RCF® (Ross Carbohydrate Free) formula + additives to provide additional carbohydrate, protein, or fat as indicated by diet calculations.
A Ketocal® formulation may be mixed with modulators such as MCT oil, beneprotein, or polydose for a customized formula.

**TABLE 32.13 Signs and Symptoms From Duke Ketogenic Diet-Metabolic Treatment Caregiver Handbook****Hypoglycemia**

- Feeling dizzy, light-headed, confused
- Having difficulty speaking
- Extreme sleepiness
- Feeling shaky, irritable, or anxious
- Being sweaty, clammy, or pale
- Racing heart beat

**Severe ketosis**

- Urine ketone test strips turn to darkest color very rapidly.
- Very irritable (more irritable than usual)
- Extreme sleepiness
- Rapid, shallow breathing
- Nausea and/or vomiting
- Facial flushing

**Dehydration**

- Dry mouth and skin
- Increased respiratory rate
- Fast heart rate
- Fever
- Sleepiness
- Urinating less often and your child's urine may be a dark yellow

**Understanding Managing Metabolic Treatment**

The main goals of management are to: (a) minimize the risk of compromising the efficacy of the therapy for seizure control, and (b) maximize the safety of patients who are in a ketotic state. In managing patients it must be kept in mind that the metabolic shift and depletion of glycogen stores produced by the treatment makes them more vulnerable to development of acute metabolic complications during times of inadequate caloric intake. The key to achieving the first goal is to avoid unintentional or excess carbohydrate exposure, which can lead to a rapid rise in blood glucose or decrease in ketone production, resulting in loss of seizure control.

KD efficacy is determined by noticeable seizure control however, the KD team also aims for target ranges of certain laboratory values. Blood glucose levels of 50 to 75 mg/dL one hour after usual meal are usually an indicator that a therapeutic level of ketosis is being established. In addition, blood ketone (ie,  $\beta$ -hydroxybutyrate) levels should be maintained at greater than 4 mmol/L, or the level at which seizures are controlled AND below the level at which the patient shows clinical signs of excess ketosis.

Meeting the second goal of safety requires close monitoring of ketone production and blood glucose levels. The goal of initiation is to establish a state of ketosis. Metabolic acidosis may be seen as treatment is initiated but usually corrects without intervention. Acidosis is not necessary for treatment efficacy. Table 32.14 shows the target ranges for the basic routine monitoring of patients on metabolic treatment.

When blood ketone levels become excessive it is usually because the energy (caloric) intake is insufficient. Inadequate energy intake is usually results from one of the following: prolonged fasting (greater than 12 hours), inadequate intake

**TABLE 32.14 Target Ranges for Routine Monitoring Labs**

- Blood glucose 50–75 mg/dL one hour after usual meal
- Beta-hydroxybutyrate >4 mmol/L or level at which seizures are controlled AND below the level at which the patient shows clinical signs of excess ketosis
- Serum bicarbonate  $\geq 20$
- Urine ketones 80–160 mg/dL or “large ketones” or 3+ ketones on an urinalysis

related to acute illness or inadequate energy in therapy prescription. It is important to remember that patients who are in ketosis do not have glycogen stores available for energy production if their prescribed dietary intake is diminished for any reason. Blood ketone levels can also become too high when the patient is dehydrated. Hydration is a very important issue because patients may experience nausea and vomiting as they adjust to the new diet, and ketosis itself can cause dehydration. Providing adequate hydration may temporarily decrease excess ketosis in patients who are dehydrated, but establishing adequate caloric intake as soon as possible is essential to prevent further increase in level of ketosis and development of metabolic acidosis. Possible signs of excessive ketosis include: lethargy, irritability, nausea, vomiting, and Kussmaul respirations.

Avoidance of symptomatic hypoglycemia is another important safety issue in KD initiation. The target range for blood glucose levels 50 to 75 mg/dL one hour after usual meal. Once established on KD therapy, patients who are well managed do not normally experience symptomatic hypoglycemia. They should only be treated for hypoglycemia

if they are symptomatic. Any unnecessary intake of glucose or carbohydrate is likely to disrupt ketosis and cause a loss of the seizure control.

In the event a patient maintained on an oral diet is unable to consume the prescribed intake and meet calorie goal, temporary feeding tube may need to be placed to prevent or treat acute complications. Some important considerations regarding the use of feeding tubes for KD therapy include the following:

- Evaluating the risk of aspiration is essential in selecting the appropriate type of temporary feeding tube to place.
- Aspiration of a ketogenic formula can result in lipoid pneumonia, which can be difficult to diagnose and treat. Lipoid pneumonia has been reported as a cause of death in patients treated with KD tube feeds.
- Nasoduodenal tubes are recommended to lower the risk of lipoid pneumonia when there is a risk of aspiration.
- When caregivers are trained and available to closely monitor patient, a nasogastric tube (NGT) may be appropriate for short-term use.
- If an NGT is used for feedings, the patient must lie at a 45 degree angle during, and 2 hours after, all enteral feeds to lower risk of aspirating the high-fat formula.

Table 32.15 lists acute complications to which patients on metabolic treatment are more vulnerable and suggested management if they arise.

### *Considerations in Initiation*

KD initiation requires close monitoring and is frequently conducted on an inpatient basis. A consensus statement from

**TABLE 32.15 Potential Acute Medical Issues in Patients on Metabolic Treatment**

PROBLEM	POSSIBLE CAUSE	POSSIBLE TREATMENT
<b>Dehydration</b> ≥5% weight loss, or fluid intake <75% fluid goal >24 h or Urine-specific gravity >1.030	<ul style="list-style-type: none"> <li>– Not meeting fluid goal</li> <li>– Increased fluid needs or losses</li> <li>– Medication</li> </ul>	<ul style="list-style-type: none"> <li>– Oral, enteral, and/or IVF total volume at 100% to 120% of calculated needs + additional fluid to correct deficit, not to exceed 240 ml/hr.</li> <li>– If IVF needed use NS, 1/2NS w/KCL or LR. No dextrose in IVF</li> </ul>
<b>Hypoglycemia (&lt;50 mg/dl)</b> Repeat bedside glucose check to confirm abnormal result	<ul style="list-style-type: none"> <li>– Missed meals/feeds</li> <li>– Inadequate calories for weight</li> </ul>	<ul style="list-style-type: none"> <li>– 1/2 usual meal or 25 ml juice</li> <li>– If symptomatic, D10 25ml x1, recheck glucose in 60 minutes</li> <li>– If &gt;12 hr NPO anticipated, once BG&lt;50 start D2.5% @ fluid goal</li> </ul>
<b>Severe ketosis (symptomatic)</b> – n/v, irritable, lethargic – May induce diuresis leading to/masking dehydration. (presence of urine ketones does not indicate severe ketosis)	<ul style="list-style-type: none"> <li>– Missed meals/feeds</li> <li>– Inadequate calories for weight</li> <li>– Intercurrent illness</li> </ul>	<ul style="list-style-type: none"> <li>– Give usual meal now</li> <li>– Assess hydration and treat if dry</li> <li>– Enteral feeds if unable to consume adequate oral intake to correct severe ketosis.</li> <li>– Parenteral Nutrition unable to use enteral route</li> </ul>
<b>Metabolic acidosis</b> Bicarbonate level <20	<ul style="list-style-type: none"> <li>– Topamax, Diamox, Zonegran</li> <li>– Missed meals/feeds</li> <li>– Inadequate calories for weight</li> <li>– Intercurrent illness</li> </ul>	<ul style="list-style-type: none"> <li>– Correct acidosis with carbohydrate-free Na- bicarb</li> <li>– Adequate fluid and energy intake.</li> <li>– If patient will not take oral → enteral feeds.</li> </ul>



TABLE 32.16 Overview of Initiation

**In-patient**

1. Typically used with higher diet ratios, ie, greater than 2:1.
2. Transition from usual food or formula to treatment at goal ratio during nearly 4 day admission.
3. Monitor for intolerance of feeds and fluid, hypoglycemia, excess ketosis, dehydration.
4. Continue patient/caregiver education as needed for competency to manage treatment at home.
5. Discharge criteria: glucose >50 mg/dL morning of discharge, large urine ketones, tolerating meals or feeds at goal, adequate fluid intake, caregiver has demonstrated understanding of treatment management.

**Out-patient**

1. Typically used for oral diet or lower diet ratios <2:1.
2. Patient or caregiver education completed before initiation.
3. Initiate by replacing one usual meal at a time with a treatment meal. Add additional treatment meal every 3 to 7 days as tolerated.
4. Caregiver to monitor for intolerance of feeds and fluid, hypoglycemia, excess ketosis, dehydration.

**Follow-up**

All patients are instructed to contact RD weekly during first month and monthly thereafter for review of efficacy and monitoring log.

the International Ketogenic Diet Study Group notes that the evidence supports the idea that the traditional initiation procedure of fasting for 12 to 48 hour before commencing intake of the KD can be eased without diminishing the likelihood of achieving a therapeutic level of ketosis (9). They state that fasting may be appropriate when a quicker time to response is desired, but is not necessary for long-term efficacy, and may have more immediate side effects. Table 32.16 summarizes KD initiation procedures employed by this institution.

The diet is started using incremental changes in the diet ratio over a period of 3 to 4 days until the full KD prescription is tolerated as illustrated in Table 32.17. Before discharge a thorough clinical examination to rule out potential acute side effects of treatment as well as a review of recent intake to confirm that the patient is meeting intake goals is essential to ensure that the patient is tolerating the treatment and is ready for discharge.

In select situations, the classic KD (ie, 3:1 or 4:1 diet ratio) can also be started in an outpatient setting, and outpatient initiation is certainly possible when a lower diet ratio has been prescribed.

TABLE 32.17 Advancing Diet Ratio During In-Patient Treatment Initiation

DAY OF ADMIT	DIET RATIO		% OF CALORIE REQUIREMENT
1	1:1	or 1:1	100
2	2:1	2.5:1	100
3	3:1	4:1	100

**Enterally fed** patients receive a mix usual formula and ketogenic formula to achieve desired ratio.

**Orally fed** patients receive Ketogenic formula and/or Keto Eggnog day 1. Solid food keto meals are introduced on day 2 of initiation.

**Diet Initiation in Status Epilepticus**

As mentioned earlier, KD therapy has also been used successfully in cases of SE. Table 32.18 outlines the approach to KD therapy that has been used effectively by the authors in a case of new-onset refractory status epilepticus (NORSE).

Other important points regarding the use and optimization of dietary therapy in SE include: (a) estimation of the total dietary caloric need should take into consideration the calories provided through the infusion of medications; (b) hypothermia decreases caloric need and should be considered when calculating dietary reference intakes for energy; (c) lowering the caloric intake below the estimated requirement can help achieve lower blood glucose and expedite seizure control.

**ONGOING MANAGEMENT**

When a stable, effective state of ketosis has been established and the patient is tolerating the diet well, discharge can proceed. However, routine monitoring must continue after discharge. Guidelines suggest clinic visits at least

TABLE 32.18 Ketogenic Diet in Status Epilepticus

- Minimize carbohydrate in medications.
- Eliminate carbohydrate from IVF.
- Ensure adequate hydration.
- Initiate treatment at diet ratio of 4:1 providing approximately 50% of estimated energy requirement with ketogenic formula.
- After serum glucose level is below 75 mg/dL, begin advancing calories. Advance calories by 10% per day to goal, if glucose remains below 75 mg/dL. If glucose rises above 75 mg/dL, then decreasing calories by 10%.
- Protein needs may not be met during initial period on treatment until sufficient calories are provided to meet calorie and protein needs while maintaining diet ratio.
- Inadequate intake and weight loss may be unavoidable initially.

every 3 months for the first year; more frequent visits may be necessary for infants or children who are at high risk for nutritional deficiency. All patients should be seen by a neurologist and dietitian with experience in managing metabolic treatment and have a nutritional assessment and laboratory evaluation.

### Routine Monitoring

Laboratory monitoring of blood values during KD therapy helps ensure good nutritional status and prevent or correct the adverse effects of the diet. Besides monitoring blood chemistries, height, and weight, the family should keep a careful seizure diary. Table 32.19 outlines follow-up monitoring to ensure optimal KD efficacy and minimize the risk of complications.

The potential complications that have been associated with KD therapy include constipation, hypercholesterolemia, hypertriglyceridemia, impaired linear growth, kidney stones, and gastroesophageal reflux. The combination of relatively small volumes of food and the diuretic effect of the KD creates the potential for constipation and kidney stones with long-term use of this therapy. Also, poor adherence to the strictly controlled calorie intake, fluid intake, and vitamin and mineral supplementation can lead to poor growth, impaired nutritional status, and seizure recurrence. Accurate measurements of growth are an essential part of monitoring, and children under the age of 2 years will require relatively frequent measurements.

**TABLE 32.19 Clinic Visits (1 mo. After Initiation, Every 3 mo. While on Treatment)**

#### Nutrition Assessment

Measure height, weight, determine BMI, growth velocity  
Review current nutrition prescription for appropriateness including calories, protein, fluid, dietary supplements, feeding regimen  
Assess compliance  
Modify nutrition prescription as needed including adjustments to diet ratio

#### Medical evaluation

Efficacy of ketogenic diet treatment  
Continue or wean KD  
Modification in AEDs or VNS

#### Laboratory Assessment

Complete blood count with platelets  
Electrolytes: serum bicarbonate, calcium, magnesium, phosphorus, zinc, selenium  
Serum liver and kidney profile  
L-Carnitine, free- and total-serum levels  
Lipid Profile  
Urinalysis  
Urine calcium and creatinine  
Serum  $\beta$ -hydroxybutyrate level  
Total vitamin D level

Abbreviation: mo, month.

**TABLE 32.20 Fine Tuning Ketogenic Diet Treatment to Improve Seizure Control**

1. Is current nutrition prescription followed consistently?
2. Is intercurrent illness having a negative impact on seizure control?
3. Has weight changed, too much or too little, and do calories need adjusting?
4. Can carbohydrate intake be decreased?
5. Can protein be decreased (only lower diet ratios providing more protein than needed)?
6. Can diet ratio be adjusted?
7. Can MCT oil be added or increased?
8. Should carnitine supplementation be added or increased?

With regular visits and ongoing communication between the patient family and the ketogenic dietitian, fine-tuning adjustments are made to the treatment plan based on changes in weight or growth, or age, well-being, and/or seizure control. Some of the options available to the ketogenic dietitian are shown in Table 32.20.

Patients and families can also monitor their own therapy. They should be encouraged to keep track of oral intake of food and fluid. Output of urine and stool should also be recorded. Illness and medication changes should be reported to the treatment team. Blood and urine ketones and blood glucose should be regularly checked. A summary of home monitoring instructions for patients and families is shown in Table 32.21.

### Managing Complications

Like all medical therapies, the KD has potential adverse effects. Overall, the risk of serious adverse events is low, and the KD does not need to be discontinued for these reasons. However, there are potential risks about which parents should be counseled. The most common acute side effects are related to inadequate intake of either fluid (eg, constipation and kidney stones) or calories (slowing of linear growth, excessive ketosis). It is important to first ask whether the patient has been fasting or not tolerating the diet well. Also

**TABLE 32.21 Home Monitoring Instructions**

- Monitor and complete log of:
  - Oral or enteral intake
  - Fluid intake
  - Stooling
  - Urine ketones (AM and PM initially)
  - Blood glucose (1–3 times per week)
  - Blood ketones (if diet ratio  $\geq$  3:1 or if using MCT oil)
  - Medication changes
  - Inter-current illness
  - Seizure activity
  - Weight

note whether or not the nutrition prescription has been reviewed within the last 30 to 60 days.

### Weaning

When patient starts KD therapy it is usually recommended that they continue with it for at least 3 months to determine if seizure control will be attained. On the other hand, successful treatment is normally continued for 2 years. Patients with GLUT-1 or pyruvate dehydrogenase deficiency who have had successful KD therapy should continue beyond 2 years. For those children who have become seizure free on the KD, 80% will remain seizure free after discontinuation. On average, the risk of recurrence after discontinuation is about 20%. However, the risk is higher for patients with tuberous sclerosis, structural abnormalities, or epileptiform EEGs. Unless there is an urgent need for discontinuation, a gradual wean over 2 to 3 months is typical. For example, a child who is on a 4:1 diet prescription will switch to a 3:1 ratio 1 to 2 weeks, then 2:1 for 1 to 2 weeks, and so on; tapering down to the point where high carbohydrate foods are reintroduced one meal at a time (13). The timing depends on individual response and the process can usually be accelerated after ketones are no longer detected.

The efficacy of ketogenic diets has been confirmed over the past 20 years, and KD therapy has achieved general acceptance as a treatment choice for epilepsy. Research into what circumstances the diet should be considered, and whether it should be considered earlier rather than later is currently under way. An increasing number of studies have been published over recent years on specific efficacy in both seizure types and epilepsy syndromes. Work is also being done on investigating more relaxed forms of the KD with an aim to improving accessibility and adherence. Data suggest that the KD could be used

in children with recently worsened focal epilepsy as an adjunct in the short term to more acute treatment.

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# Alternative Therapies

William L. Bell

What is considered mainstream versus alternative therapies in medicine is very dependent on time and geography. The late nineteenth-century classic texts by Gowers and others cite various salts of bromide as the accepted treatment for human epilepsy, with a variety of medications including *Cannabis indicus* (tincture) mentioned as alternative treatments (1). Today alternative treatments are often called complementary as they complement rather than replace modern medical therapies. Complementary and alternative (CAM) therapy may seem new, but many of these treatments are traditional remedies in other cultures going back several thousand years. These therapies are the accepted primary healthcare by those whose access to modern medicine is limited by a host of geographic, economic, cultural, or religious factors. A 2002 survey of U.S. adults found that when megavitamin therapy and prayer were included, 62% had used at least one CAM therapy in the past 12 months. When megavitamin therapy and prayer were excluded, the number fell to 35%, but this still represents more than a third of Americans (2). A similar percentage of surveyed patients in epilepsy centers use CAM for the treatment of epilepsy and other ailments (3,4). Many of these patients did not inform their physicians that they were using CAM, an important finding considering that many herbal remedies have significant interactions with antiepileptic drugs (AEDs) (3).

As we consider various categories of CAM, it is important to note that few randomized controlled trials exist and the ones that exist are not double-blind studies. For the controlled trials that have been accomplished, the numbers in each treatment and control group were small, making the studies difficult to interpret.

## MIND-BODY THERAPIES

Patients frequently report an increase in seizures during times of stress, sleep deprivation, and fatigue. In general, idiopathic generalized seizures are prone to be increased by sleep deprivation and partial seizures by stress (5). These factors are part of life and many neurologists have had the experience of admitting patients to epilepsy monitoring

units with well-documented frequent seizures, but after admission these patients have few events even with medication reduction. This may be a clue as to how much the stresses of everyday life affect seizure frequency. Therefore, it is natural to look at means to mitigate stress and other factors in patients.

## Prayer

Although prayer is not always considered CAM, in a survey of epilepsy patients in Arizona, prayer and stress management techniques were the most common methods used, followed by herbal supplements (4). Similar findings were found in a survey of 149 epilepsy patients in Kansas with prayer/spirituality (41%) most common followed by “mega” vitamins (22%), chiropractic care (21%) and stress management (14%). Thirty-six patients used prayer/spirituality specifically for their epilepsy and 33 (89%) reported benefit (3). However, there are no controlled studies for prayer and epilepsy and this is a difficult arena to design a study. What constitutes healing prayer varies significantly between faiths in the Western traditions.

## Yoga and Meditation

In a review of 82 studies that attempted to measure the efficacy of meditative techniques, the studies with the most dramatic results were those using Sahaja yoga for the treatment of epilepsy. One study randomized patients into three groups: 6 months of Sahaja yoga, 6 months of exercises mimicking Sahaja yoga, and 6 months of neither. In the first group, there was an 86% reduction in seizures with no improvement in the other two groups (6). These results have not been replicated. There are many varieties of yoga, and Sahaja yoga emphasizes the dhyana or meditative components. Hatha yoga is a more eclectic type of yoga that includes a variety of yoga components, but there is more of an emphasis on physical postures and is one of the most common types of yoga practiced in the United States. A study comparing Hatha yoga and routine exercise in epilepsy patients showed improvement



in parasympathetic parameters and a reduction in seizure frequency in the yoga group but not the exercise group. Adverse effects are uncommon, but yoga participants should be in good physical condition and aware of their skill levels to avoid overstretching, strains, and fractures. Inverted poses can increase intraocular pressure, worsening glaucoma (7). Finally, yoga may not appeal to patients who are put off by yoga's connections to Hindu and Buddhist spiritual traditions.

Transcendental meditation (TM), although derived from ancient yogic teachings, deserves separate mention as the most popular form of New Age meditation. Trademarked by its founder Maharishi Mahesh Yogi, it is officially nonreligious, although one of its goals is to attain "God Consciousness." Along with postures and breathing exercises, the participants enter into a trance by allowing an assigned secret sound or mantra to overcome the mediator's thoughts. It differs from other techniques in that it is highly standardized and teachers must be certified. There have been anecdotal reports of seizures provoked by TM and others report benefit with a reduction of seizures. However, there have been no controlled clinical trials (8).

Mindfulness meditation and mindfulness-based stress reduction, which pair meditation with yoga, are popular mind-body therapies developed by Jon Kabat-Zinn, but there are no controlled studies for the treatment of epilepsy (6). Christian meditation has a history that goes back centuries and continues to thrive in both Protestant and Catholic circles. Also known as centering prayer, it has been used in the management of depression, but not for neurologic disorders.

### Relaxation Therapy

Progressive muscle relaxation was developed by Edmund Jacobsen in the 1920s. The patient tenses and releases sequentially muscle groups one at a time. The tension phase should be 10 to 20 seconds and the relaxation phase should last 20 to 30 seconds. This is practiced for 20 minutes twice a day in a comfortable and quiet environment. In one small controlled study, 13 patients with progressive relaxation had a 29% reduction in seizures compared to the control group of 11 patients with quiet sitting who had a 3% reduction. With only a limited number of individuals studied, no definite conclusions can be made (9).

### Self-Control and Counter-Measures

Many patients identify common situations in which they tend to have seizures. Patients surveyed by Dahl found that seizures followed drowsiness (84%), physical activity (83%), negative stress (78%), muscle tension (71%), demanding situations (67%), and panic (64%). Sixty-nine percent of patients thought that they could reliably trigger a seizure by such means as hyperventilation, imitation of seizure movement or thoughts, and by intermittent periods of high-energy physical activity followed by sudden rest (10).

Application of countermeasures to prevent or limit seizures goes back to the first and second centuries. A ligature was placed around a limb with a sensory aura to prevent the spread of a seizure. It was thought the ligature could keep a seizure-triggering humoral substance from spreading like venom. Such countermeasures continued into late nineteenth century with Gowers recommending a variety of countermeasures: ligature proximal to convulsion, forcible prevention of spasm, cutaneous stimulation, activity such as walking around room, strong olfactory and gustatory stimulation (1). In Dahl's study, patients with simple partial seizures developed countermeasures spontaneously including restraint of motor movement (74%), stimulation of the area of sensation (77%), stimulation using auditory (85%), olfactory (32%), or visual stimuli (22%). Also sometimes effective were applied relaxation in 78% and/or using positive statements in 89%. For those with complex partial seizures, they spontaneously used restraint of motor automatism in 78% and general arousal in 57% using a variety of sensory stimuli. Many of the author's patients report that a family member can limit the extent of the seizure through verbalization or touch. Discovery of countermeasures can be facilitated by the ABC method according to Fenwick. "A" is for antecedent experiences that occur before seizure onset. If there are some common experiences before a seizure, perhaps a countermeasure could be designed to address those experiences. "B" is for behavior. A patient who felt that a simple partial seizure would engulf him, he could snap a rubber band on his wrist resulting in pain so as to maintain control of the seizure. "C" is for consequence (10). For example, could a patient be rewarded or punished in any way for having a seizure? Whether this knowledge helps control seizures or not may be debatable, but learning of psychosocial consequences is useful for managing the patient. The author had a patient who was embarrassed at school by excessive attention paid to her seizures by teachers and school staff. This led to an aversion to going to school and eventually homebound instruction even though the seizures themselves were not frequent or disruptive. Countermeasures have been more systematically studied as part of comprehensive neurobehavioral programs.

### Reflex Epilepsies

In the official International League Against Epilepsy (ILAE) classification of epilepsies, reflex epilepsies are placed in a special category regardless of whether focal or generalized and characterized by specific types of provocation. Once the patient can identify seizure precipitants, they may be able to avoid those stimuli. The precipitants may be more likely to trigger a seizure when the patient suffers stress or lack of sleep. Many different stimuli have been described, including listening to music, eating, bathing, calculating, thinking, and decision making. Photosensitive patients report more seizures evoked by flickering lights or videogames, following sleep loss and some authors have reported increased EEG photosensitivity after sleep deprivation. Photosensitive epilepsy is

the most common type of reflex epilepsy. Preventive measures include avoiding videogames, certain types of video and computer screens, and environments with flashing lights. Wearing blue-colored lens (Zeiss Clarlet F133 Z1) and covering one eye may help prevent seizures with the approach of potentially provocative visual circumstances (5). The author had a patient who tinted his car windows successfully limiting the effect of sunlight flashing through trees. Unfortunately, he ran afoul of his jurisdiction's window tinting law.

### Biofeedback

Biofeedback is a treatment in which physiologic parameters normally hidden from conscious awareness are measured and displayed back to the patient such that the parameter comes under conscious control. Using galvanic skin response biofeedback, there was a modest reduction of seizures in a single-blind, randomized controlled study of 18 patients with 10 biofeedback active and 8 sham controls. Six of the 10 patients showed a 50% or greater reduction in seizures. EEG biofeedback also known as neurofeedback has been used for many years in experimental protocols for the treatment of epilepsy, but studies have been small and not properly controlled. The desired parameter usually is a sensorimotor rhythm typically ranging from 12 to 14 Hz. When the rhythm is present, a reinforcing visual or auditory stimulus is given to the patient. In a meta-analysis of 243 patients from 24 studies, about 82% of patients showed a 50% reduction or greater reduction in seizures. For the different studies the training sessions ranged from 60 to 90 minutes and occurred one to three times a week over 6 to 24 weeks. This requires extensive commitment and may not be practical for many patients (9,11).

### Comprehensive Neurobehavioral Programs

There are programs that use a variety of techniques to reduce seizures. Some of these techniques have already been discussed. The Andrews/Reiter (A/R) program starts with obtaining a history of seizure onsets, emotions, and circumstances similar to Fenwick's ABC method. Patients are also taught techniques to lower internal stress by including progressive relaxation and deep breathing exercises to use at seizure onset. Biofeedback using EMG and EEG is also used to reduce seizures. Finally, patients are given cognitive and behavioral counseling and asked to set life goals (12).

Acceptance and commitment therapy (ACT) is a structured program that is an extension of cognitive behavior therapy, but with links to relational frame theory. The first step for patients is acceptance of aspects about their epilepsy that they cannot change. The goal of the therapy is to create a psychological flexibility and to broaden the patient behavioral repertoire to be able to accomplish chosen values and life goals. Another meaning of ACT is: accept, choose and take action. Patients learn to distinguish themselves from life experiences including their seizures. ACT protocol consists of individual and group sessions. In one randomized

controlled study ACT was combined with seizure control countermeasures that were individualized to each patient to serve as the active arm (14 patients). The control group (13 patients) received supportive therapy where therapists created an empathetic and accepting environment where patients could reflect on their lives and problems. Both study conditions included both individual and group sessions. There was a significant reduction in seizure frequency and duration with improved quality of life in the ACT group when compared to the supportive therapy group (9).

### MANIPULATIVE AND BODY-BASED THERAPY

Chiropractic is one of many body-based therapies and medical systems. Since its beginnings in the Midwest in the United States in the late nineteenth century, chiropractic has an important, albeit contentious role as a health profession. As of 2000, there were 65,000 chiropractors in the United States and 90,000 worldwide. Ninety percent of patients seek help from a chiropractor for neuromusculoskeletal complaints, mainly back pain, neck pain, and headaches (13). With the prevalent use of chiropractic, it is not surprising that a significant percentage of patients with epilepsy have used chiropractic. In the previously mentioned Arizona survey, 44% of epilepsy patients had used chiropractic, with 38 (10%) using it specifically for seizure control and 16 patients claiming benefit (4). There have been anecdotal reports of epilepsy benefiting from chiropractic care, but no controlled trials. Other manual therapies classified under energy medicine have been used in epilepsy.

### ENERGY MEDICINE AND TRADITIONAL ASIAN MEDICINE

#### Traditional Chinese Medicine

Yin and yang are fundamental concepts in Chinese philosophy and in traditional Chinese medicine (TCM). According to these concepts, within every natural object there are two interacting energy-modes, the yin and the yang. Yang is active, warm, dry, bright, and procreative. Yin is passive, cold, wet, dark, and mysterious and fertile. Yin and yang express two opposing but complementary phenomena that are in dynamic equilibrium. In the human body, when there is an alteration in this equilibrium disease occurs. Also the human body is composed of five phases or elements: wood, fire, earth, metal, and water. Another important concept is *qi* sometimes translated as energy. *Qi* is what flows and nourishes; it is closely linked with blood. The therapeutics of TCM mobilize and regulate the movement of *qi* in the body. One method is acupuncture. Important to this method is the idea of channels and points. There are 12 primary and 2 extraordinary channels and *qi* is understood to flow through these channels. Along the pathway of the channels are specific points and needles are placed in these points as much as an inch below the skin. Based on the concept that all disease involves the disruption of the flow of *qi* theoretically, any

**TABLE 33.1 Traditional Chinese Medicine**


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Acupuncture
Moxibustion
Cupping and bleeding
Chinese massage
Qi cultivation
Chinese herbal medicine
Dietetics

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disease can benefit from acupuncture and related treatments including a proper diet (Table 33.1). The aim of the acupuncturist is to obtain *qi* at the site of the needle insertion. The *qi* is felt either objectively or subjectively (13). Despite anecdotal case reports and some interesting animal studies purported to show a mechanism, studies have not shown much benefit. In a Cochran review of acupuncture treatment comparing acupuncture to phenytoin and in another study comparing acupuncture to valproate, there were no consistent differences between the groups. In the only trial where a sham control was used, 29 patients randomized to acupuncture or sham acupuncture, there was a modest reduction in seizures in both groups, but the reduction was not statistically significant (14).

Herbal treatment in TCM generally consists of a complex formula of several (eg, 6–20) components. The treatments are chosen based on TCM diagnostic patterns and theory with a rationale quite different from many Western drug treatments. One of the herbs called the *ruler* sets the therapeutic direction of the formula. The other herbs are used to treat additional symptoms and signs that are considered part of the main disease process (13). Often the active chemical ingredient is not actually known, but in the case of formulas for epilepsy some have been found to be active in animal models of epilepsy. “Qingyangsen” root was found to be active in small clinical studies and in a kainic acid-induced mouse model (15). An extensive review of TCM controlled studies for herbal treatment of epilepsy found that studies were of poor quality based on current standards of study design. However, they found five studies with a design sufficient for analysis. Although some formula components were the same between studies, most of the formulas had very different components. Banxia (*Rhizoma pinelliae*) was a component in four out of five studies. Changpu (*Acori graminei*), fuling (Poria), and quanxie (Scorpio) were other constituents common between studies. Three of the studies compared the herbal formula to phenytoin, one compared a formula to valproic acid and one compared a formula to phenobarbital. Four of the five studies demonstrated either equivalency or superiority of the TCM herbal treatment to the more standard antiepileptic drugs (AEDs) for some parameters, but significant methodological problems limit reliable conclusions concerning the role of traditional Chinese herbal treatment for epilepsy (16).

### Japanese “Kampo” Medicine

Japanese “Kampo” medicine derives from Chinese medicine. Cultural exchanges between China and Japan began in the first century and Chinese influence on Japanese medicine was firmly established by the early eighth century. In general, herbal prescriptions contain lower dosages compared to those used in Chinese medicine (13). It is estimated that 70% of “Western” physicians prescribe kampo drugs on a regular basis in Japan. The most common medicine used for seizures is TJ-960, which is a mixture of nine herbal drugs, *Bupleuri radix*, *Cinnamomi cortex*, *Ginseng radix*, *Glycyrrhizae radix*, *Paenoniae radix*, *Pinelliae tuber*, *Scutellariae radix*, *Zingiberis rhizome*, and *Zizyphi fructus*. In one study where 26 patients received TJ-960 compared to 17 controlled, the authors concluded benefit from the herbal mixture. However, with only a third of the TJ-960 patients showing a 25% reduction in seizures, the results appear to be modest (15).

### Indian Ayurvedic Medicine

Ayurveda means “science (veda) of life (ayu)” when translated from Sanskrit. In Ayurveda, there is a significant emphasis on prevention. Ayurvedic practitioners recommend that patients with seizures adopt specific lifestyles and dietary practices including taking herbal preparations. The most common preparations include Ashwagandha, Brahmirasayan, and Brah-migritham. These herbs are part of the polyherbal preparation of BR-16A (Mentat), which is widely used along with allopathic AED treatment in current Indian medical practice and reported to be of value in alcohol-withdrawal seizures (15,17).

### Reiki and “Energy Therapies”

Reiki, healing touch (HT), and therapeutic touch (TT) are energy therapies where a practitioner uses hand techniques to help mold and rebalance the patient’s energy field to promote healing of the body. These therapies promote healing and are not designed to specifically treat diseases. TT and HT were founded by nurses. In TT the hands do not actually touch the body, whereas in HT they do. In both TT and HT there is active evaluation and intention to affect the energy field. Reiki was developed in Japan in the 1920s. There is no evaluation or intent to repattern the energy field in Reiki. Rather, Reiki practitioners believe that they can impart energy through their hands according to what the patient needs. While there have been no known adverse effects, these techniques have been met with skepticism. Reiki-like healing practices were used in a small number of epilepsy patients over 3 months with a decrease in seizure frequency, but the study had serious methodological problems (13,17). There have been no studies on TT or HT in epilepsy.

### Homeopathy

Samuel Hahnemann (1755–1843) developed homeopathy based on certain principles. One is that remedies derive from



natural substances prepared through a process of serial dilution alternating with vigorous shaking or succession to the extent that not a single molecule of the original substance remains. It is by this process it is believed that bioenergy is transferred from the original substance to the solvent. The other principle is that the minimum dose of a substance can be used to cure the symptoms that would be caused by a much higher dose of the same substance. Homeopathic remedies used in epilepsy are not based on seizure types or etiologies. Rather, remedies are chosen based on many factors, including seizure semiology, symptoms preceding seizures, and the types of triggers without regard to therapeutic principles in allopathic medicine. In addition, remedies depend on many physical characteristics of the patient unrelated to the seizures. There are no controlled trials using homeopathic remedies in epilepsy and trials could be difficult to design since homeopathic treatment is not disease or syndrome specific (17).

HERBAL MEDICINE

Introduction to Herbs

It is estimated that at least 25% of medications used in conventional treatments originated at least in part from plants. Common examples include ergot from the fungus *Claviceps purpurea*, digitalis from foxglove (*Digitalis purpurea*), and atropine from deadly nightshade (*Atropa belladonna*). This fact has been used to promote support for herbal treatments. In the United States, herbal medicines are currently classified as dietary supplements based on a law passed by the U.S. Congress in 1994. Therefore, herbal medicines do not have the same manufacturing and quality standards that are required for conventional drugs that can be regulated by the Food and Drug Administration (FDA). Europe has taken a different approach with more exacting potency and purity standards. Herbal drugs sold as dietary supplements in the United States are often sold as prescription medications in European countries. Actual amounts and potency of dietary supplement may vary widely depending on plant species, season of harvesting, and plant parts used. One study on feverfew, an herb used for migraine headaches, found that 22% of the products tested contained no feverfew. To complicate matters further, some herbal preparations were found to have contamination with unlabeled drugs and toxins, such as heavy metals (18).

With the lack of potency standards, the absence of clinical trial data supporting use of specific herbs, and the unpredictability of toxic effects, the neurologist may well decide against recommending medicinal herbs. However, many patients are already using herbal medication and a minority report this use to their physicians. One survey reports that one in six adults in the United States who take prescription drugs also uses at least one medicinal herb (19). Therefore, it is important for every neurologist to ask specifically about herbal medication. Besides questions of efficacy and potential toxicity, herb–drug interactions are common.

Determining what herbs the patient is actually using may be a challenge as the same herb may have many different generic names and the label often does not have the scientific name of the plants used.

Herbs for the Treatment of Epilepsy

It may not be surprising that some herbs used to treat seizures have known sedative effects (Table 33.2) Valerian (*Valeriana officinalis*) root, best known for its sedative properties, is the most common herb prescribed for epilepsy throughout history. While there is no proof of its efficacy in either human or animal studies of seizures, it could exert direct therapeutic effect or indirect effects by sedation and by the promotion of sleep.

Kava (*Piper methysticum*) is another anxiolytic herb used to treat epilepsy. However, it is not without significant side effects. Twenty-four cases of hepatotoxicity were reported in Germany and Switzerland with several requiring liver transplants. With high doses there may be anorexia, hearing loss, hair loss, and the skin may become dry, flaky, and exhibit a yellowish discoloration. These effects have been mostly observed in patients from the South Pacific where kava is used as a ceremonial and recreational beverage. Also, kava should not be used along with alcohol or other sedative medication as potentiation may result in excessive sedation.

Black cohosh (*Cimicifuga racemosa*) is a plant whose root may be used for menstrual and premenstrual symptoms. It also has sedative properties and has been used for the treatment of seizures. However, it may potentiate the effects of antihypertensives resulting in hypotension. Mistletoe (*Viscum sp.*), American Hellebore (*Veratrum viride*), and Scullcap (*Scutellaria laterifolia*, *S. baicalensis*) are also used to treat seizures, and have both anticonvulsant and proconvulsant effects.

Marijuana (*Cannabis sativa*) has become a frequent topic of discussion in the clinical setting with many patients claiming benefit from its use. The plant contains at least 60 active substances, including THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol), which is less psychoactive compared to THC. While there is evidence that components of marijuana may have antiepileptic properties in animal studies, the evidence is much less clear in human epilepsy. Reports are conflicting as to whether seizures frequency is affected, but there is evidence that sudden withdrawal after

TABLE 33.2 Herbs Used in the Treatment of Epilepsy

Valerian ( <i>Valeriana officinalis</i> ) root
Kava ( <i>Piper methysticum</i> )
Black cohosh ( <i>Cimicifuga racemosa</i> )
Mistletoe ( <i>Viscum sp.</i> )
American Hellebore ( <i>Veratrum viride</i> )
Scullcap ( <i>Scutellaria laterifolia</i> , <i>S. baicalensis</i> )
Marijuana ( <i>Cannabis sativa</i> )



regular use of marijuana may precipitate seizures (12). CBD is available in several areas of the United States. In a survey of 18 California parents who were using CBD for their children, many with severe epilepsy including 12 children with Dravet syndrome, 15 of the 18 parents reported seizure reductions. Eleven children had greater than an 80% seizure reduction (20). Randomized trials so far have had small numbers of subjects and were otherwise of low quality. Therapeutic potential of cannabinoids has been complicated by availability of synthetic cannabinoid (K2/Spice) as a popular alternative to marijuana with significantly more adverse events that include tachycardia, chest pain, hallucinations, and seizures (21).

### Herbs Known to Provoke Seizures

Ephedra (*Ephedra sinica*) also known as *ma huang* in China has been used as a traditional medicine for thousands of years. In Chinese medicine, it is used for arthralgia, asthma, colds, cough, edema, headaches, and nasal congestion. Ephedrine is the main active ingredient. It has stimulating effects and mimics the effects of norepinephrine. Ephedra is known to provoke seizures even in patients without a past history when combined with other stimulants such as caffeine (Table 33.3). Studies of herbal *ma huang* products have shown considerable variation of ephedra alkaloids amounts between brands and even within the same brand. The ephedra-caffeine mixture is also known as herbal ecstasy, which is commonly used at “rave” parties.

Ginkgo (*Ginkgo biloba*) may be the most popular herb used in the United States. Its primary use is to improve memory. In surveys of patients with epilepsy, it is commonly used sometimes explicitly for seizure management. However, it contains the neurotoxin 4'-O-methoxypyridoxine (MPN), which inhibits GABA formation. Seizures have been reported during its use; but with the large number of people taking this herb, more reports would have been expected. Regardless, since Ginkgo's memory benefits are questionable, it is best avoided in patients with epilepsy.

Evening primrose (*Oenothera biennis*) is a popular herb used for premenstrual syndrome, Sjögren's syndrome,

and diabetic neuropathy. Primrose contains omega-6-fatty acid-linolenic acid (GLA), which can lower the seizure threshold. The herb Starflower or borage (*Borago officinalis*) also contains GLA and should also be avoided in patients with epilepsy.

Essential oils are extracts from a variety of plants and used for aromatherapy or massage. If ingested, inhaled, or even absorbed through the skin, there may be toxic effects. Most concerning for provoking seizures are eucalyptus (*Eucalyptus globulus*), fennel (*Foeniculum vulgare*), pennyroyal (*Mentha pulegium*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), and wormwood (*Artemisia absinthium*).

Other seizure-provoking herbs include Japanese star anise (*Illicium anisatum*) containing the neurotoxin anisatin, a potent noncompetitive GABA antagonist, and the Chinese star anise (*Illicium verum*), generally safe but in high concentrations, can trigger seizures. These herbs are not to be confused with Star fruit (*Averrhoa carambola*), which is a tropical fruit containing large amounts of oxalic acid, that has been responsible for severe neurotoxicity including status epilepticus in patients with moderate renal failure (12,15,19).

### Herb-AED Interactions

Herbs and even some foods may affect AED pharmacokinetics. Most of the effects are seen via the P450 enzyme system. St. John's wort has been reported to reduce the levels of cyclosporin, warfarin, oral contraceptives, theophylline, and the protease inhibitor indinavir. There are potential interactions with AEDs based on CYP induction by St. John's wort, but so far none has been reported. Other herbs that have an inhibitory effect on the P450 enzymes include echinacea, garlic, milk thistle (*Silybum marianum*), Mugwort (*Artemisia vulgaris*), and Pipsissewa (*Chimaphila umbellata*). Foods that may inhibit the P450 system include grapefruit juice and broccoli. A large glass of grapefruit juice can significantly increase the oral bioavailability of carbamazepine and diazepam. P-glycoprotein (Pgp) is a membrane transport system that moves substrates out of cells. This system affects the intestinal absorption of the AEDs as well as their delivery into the CNS. Herbs that cause inhibition of this system include St. John's wort, garlic, pycnogenol, and pippissewa. Pharmacodynamic interactions may be responsible for herbs that potentiate the action of certain drugs such as when kava potentiates the effects of alcohol, benzodiazepines, and barbiturates (12,19).

**TABLE 33.3 Herbs that Provoke Seizures**

Ephedra ( <i>Ephedra sinica</i> )
Ginkgo ( <i>Ginkgo biloba</i> )
Evening primrose ( <i>Oenothera biennis</i> )
Starflower or borage ( <i>Borago officinalis</i> )
Eucalyptus ( <i>Eucalyptus globulus</i> )
Fennel ( <i>Foeniculum vulgare</i> )
Pennyroyal ( <i>Mentha pulegium</i> )
Rosemary ( <i>Rosmarinus officinalis</i> )
Sage ( <i>Salvia officinalis</i> )
Wormwood ( <i>Artemisia absinthium</i> )
Japanese Star anise ( <i>Illicium anisatum</i> )
Chinese star anise ( <i>Illicium verum</i> )
Star fruit ( <i>Averrhoa carambola</i> )

With few quality randomized controlled trials (RCT), it is difficult to make evidence-based recommendations on the use of alternative treatments for epilepsy. There was a time in medicine when RCT were neither expected nor required. So as conventional practitioners, are we setting too high a standard? There are few opportunities for any of these treatments to become patentable and so industry funding is unlikely. Herbal treatments may well be the most problematic for the neurologist to adopt. Even

though some herbs show activity against seizures in animal models the lack of purity standards in North America complicates the interpretation of the current literature and the initiation of RCT. Potential for toxic side effects and herb–drug interactions further cloud any optimism for use of herbal medication. TCM, Japanese, and Indian medicine practitioners have more experience in the use of herbal treatments and may know how to use them with a greater degree of safety.

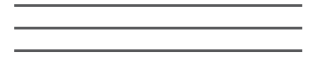
Most neurologists already consider lifestyle changes important in the treatment of epilepsy. Closer attention to precipitating factors in reflex epilepsy and incorporation of countermeasures for partial epilepsy appears to be safe and effective. In contrast, except as a component of traditional Asian medicine, “energy therapies” have a limited rationale and no evidence of benefit in the treatment of epilepsy. Biofeedback is safe and may be effective, but requires extensive training, which may make it impractical. Incorporation of relaxation techniques, yoga, and meditation is for the most part safe although efficacy remains unproven. Comprehensive neurobehavioral approaches seem to hold significant promise by combining countermeasures, cognitive behavioral therapy, and other techniques.

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P A R T



# Special Situations





# Status Epilepticus and Frequent Nonconvulsive Seizures

*Keith E. Dombrowski*

Status epilepticus (SE), particularly generalized convulsive status epilepticus (GCSE), is a common problem encountered in the United States and worldwide. In the simplest terms, SE is defined as the occurrence of incessant seizures without recovery in between. The International League Against Epilepsy (ILAE) defines SE as “a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of the type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally.” There are as many forms of SE as there are types of epilepsy. Of the various types of SE that are known, GCSE is the most common with an annual incidence of approximately 150,000. When considering the other forms of SE, the true incidence of SE is significantly higher. Though morbidity and mortality depend on the form of SE, current mortality estimates of GCSE are approximately 35%, with an additional 13% left with severe neurologic deficits (1). SE has been a known entity for much of human history but only in the past century have effective treatments been developed. EEG and now continuous EEG (cEEG) monitoring has helped define and shape diagnostic and treatment algorithms (2). Similarly, the development of emergency medical services and critical care has also played a significant role in effectively treating SE.

## NOMENCLATURE

The impact of SE on the patient depends on the type and etiology of SE. GCSE carries the greatest risk for death and disability. Morbidity and mortality in nonconvulsive status epilepticus (NCSE) differs significantly based on the underlying etiology. NCSE is a broad term that encompasses absence SE, forms of simple and complex partial SE (CPSE), as well as NCSE in the critically ill. Absence or atypical absence status epilepticus appears to be a benign diagnosis that can be treated with oral medications in most cases. By contrast, focal status epilepticus or *epilepsia partialis continua* (EPC) that is caused by a brain tumor or abscess probably has a worse prognosis. NCSE in the critically ill is associated with worse neurologic outcome and is probably associated with neuronal injury.

## ABSENCE STATUS EPILEPTICUS

Absence SE (ASE) is generally associated with idiopathic generalized epilepsy, including typical absence epilepsy and juvenile myoclonic epilepsy (JME). Other forms of ASE include atypical absence SE as seen in symptomatic, generalized epilepsy such as Lennox-Gastaut syndrome. Semilogically, ASE or atypical ASE is a subtype of NCSE, but there appears to be no association with resultant neuronal damage or increase in death or disability as a result of its occurrence. ASE has been defined as a state of altered consciousness, often with brief eyelid or limb jerking, that occurs in those with idiopathic or symptomatic generalized epilepsy and is associated with generalized spike and wave (GSW) EEG activity. Typical ASE is associated with 3 Hz or faster GSW, whereas atypical ASE is associated with slower GSW (less than 2.5 Hz). There are numerous reports of *de novo* ASE that can occur in the elderly and other cases that are situational or are provoked, such as in cases of benzodiazepine withdrawal (3). Treatments can be specific to the disorder in certain cases, but the first-line treatment for most cases of ASE will consist of intravenous benzodiazepines followed by phenytoin or valproic acid (VPA). Ethosuximide or VPA would both be reasonable choices for typical ASE, as either would likely be the maintenance drug of choice. VPA would be a reasonable choice in a patient with JME. The utility of new anticonvulsants is unknown and would be determined by the responsiveness of individual patients.

## FOCAL STATUS EPILEPTICUS

Focal SE (FSE) can include a wide variety of prolonged (greater than 30 minutes) clinical manifestations, including repetitive focal motor, sensory, and myoclonic activity as well as uncommon cases of aphasia and visual loss. EPC is a type of motor FSE that consists of recurrent focal motor seizures that are often myoclonic but can consist of repetitive dystonic movements that can continue for days, week, or even years. In less common circumstances, FSE can be associated with an alteration in mental status, which is

sometimes seen in patients with subdural hematomas and rarely in those with an orbitofrontal focus. The etiology of these conditions is typically from focal cerebral pathology, including tumor, trauma, and particularly stroke in the elderly. In children and young adults, Rasmussen's encephalitis should certainly be considered as a cause (4). However, some diffuse conditions like nonketotic hyperglycemic hyperosmolar state and mitochondrial encephalopathies can be associated with FSE. These conditions can be difficult to diagnose depending on the presentation and are often frustrating to treat due to a variable pharmacologic response. cEEG monitoring is often helpful in confirming the diagnosis, but electrographic seizures often do not have a scalp EEG correlate due to very restricted foci of seizure activity. The utility of intracranial EEG monitoring is unknown but may be helpful in some circumstances. In many cases, the diagnosis of FSE may be entirely clinical or substantiated by functional imaging such as PET or SPECT to identify hypermetabolic areas of the brain. Pharmacologic control of FSE, particularly EPC, can be difficult and frequently require multiple medications. Little is known about the individual efficacy of different anticonvulsants, but topiramate and levetiracetam may be effective (5). Complete resolution of the seizures may not be possible in some circumstances or may require aggressive treatment such as hemispherectomy in Rasmussen's encephalitis to prevent seizures and progression of the underlying disease. Surgical options should also be considered in other patients who have had refractory seizures caused by a focal lesion such as an abscess, tumor, or hematoma. The outcome of patients with FSE is variable and depends on the underlying condition that is associated with the FSE. Although focal sensory symptoms may not lead to further neuronal damage, focal motor SE in Rasmussen's encephalitis is strongly correlated with outcome.

## GENERALIZED CONVULSIVE STATUS EPILEPTICUS

### Epidemiology

GCSE is the most common form of status epilepticus with 150,000 reported cases per year. The estimated financial cost of GCSE is nearly \$4 billion per year. The human cost is hard to define, but the mortality is approximately 25% to 30% with estimates as high as 60% in refractory (RSE) or super refractory SE (SRSE) cases. RSE has been defined as SE requiring initiation of anesthetic medications and SRSE is persistent status epilepticus after 24 hours of anesthetic administration. SE is most common at the extremes of age, with the highest incidence in children less than 1 year and adults over 60. Age is also a significant predictor of mortality with highest reported number of deaths in the elderly (1).

### Etiology

Most patients who develop status epilepticus have a history of epilepsy and the most common reason to develop SE is

medication nonadherence. The majority of patients with epilepsy will not experience SE during their lifetime but many others will have SE as their presenting symptom of epilepsy. Other common causes of SE include cerebrovascular disease, other forms of remote brain injury, anoxic injury, alcohol, and drug withdrawal as well as metabolic dyscrasias. In the hospital, toxic-metabolic causes of SE are common and are associated with the administration of medications that lower seizure threshold (ie, certain antibiotics, antipsychotics, and anesthetics), systemic infection, and electrolyte disorders like severe hyponatremia and hypoglycemia. Drug or alcohol withdrawal seizures are especially common in the hospital including SE from benzodiazepine withdrawal. The etiology of the GCSE is significantly associated with outcome. Those with a history of epilepsy, seizures as a result of drug or alcohol withdrawal, and those with a chronic stroke have the best prognosis. Those with the worst prognosis include the critically ill patients especially those with sepsis, acute brain injury, anoxic-hypoxic injury, the elderly and those with multiple medical comorbidities. Those with refractory or super refractory SE also experience significant morbidity and mortality. The most common cause of refractory SE is likely anoxic-ischemic encephalopathy or CNS infection. In recent years, new-onset refractory and super refractory cases of SE (NORSE) have been reported in patients without a prior diagnosis of epilepsy. These patients may have a viral prodrome before the onset of seizures or in some cases prominent psychiatric symptoms before seizures begin. New-onset refractory cases are thought to be related to a viral encephalitis or autoimmune encephalitis. Unlike the more common causes of SE, it is very difficult to control seizures even with numerous anticonvulsants and anesthetic agents. As a result, the morbidity and mortality of NORSE cases is high (6).

### Definition and Stages

Traditionally, GCSE has been defined as the occurrence of continuous seizure activity for 30 or more minutes, or more than two generalized seizures within a 30-minute period without recovery in between. However, a more practical definition is of continuous seizure activity lasting greater than 5 minutes or frequent clinical seizures without evidence of recovery in between. GCSE can consist of different types of generalized activity including tonic-clonic, tonic, clonic, or myoclonic seizure activity. Bilateral motor activity is common, but in many cases, motor activity can be seen predominantly on one side or the other. Generalized myoclonic SE is another form of GCSE and it has particular implications in postcardiac arrest patients. In most patients, particularly those who have not undergone therapeutic hypothermia, it is associated with a dismal prognosis. As a result, treatment is often directed at symptom management rather than suppression of electrographic seizures.

Though convulsive activity defines GCSE, these movements frequently terminate or degenerate after several minutes regardless of whether treatment is initiated or not. Due

to responsive emergency medical services who administer benzodiazepines in the field, many cases of status epilepticus will be treated before arrival to the hospital. In cases where SE has not been adequately treated, generalized convulsions give way to subtle status epilepticus or nonconvulsive status epilepticus after several minutes. In these cases, the patient remains obtunded or comatose and may only have evidence of subtle limb jerking or eye movements even while electrographic seizure activity continues unabated. Without cEEG monitoring, it will be nearly impossible to tell whether the patient is continuing to have electrographic seizures or this activity has stopped. Urgent treatment remains a priority for these patients as the duration of SE is linked to the outcome of the patient. Diagnosis and treatment of nonconvulsive seizures is critical to prevent further neuronal injury (7).

Though some variation is expected, animal models and an increasing amount of human data accurately describe the natural history of SE physiologically, clinically, and electrographically. Physiologically, SE is initially characterized by an increased cerebral metabolic rate that is coupled with increased cerebral blood flow (CBF). Increased CBF is met by increased cardiovascular parameters and increased anaerobic respiration. However, metabolic decoupling rapidly occurs after several minutes as cerebral autoregulation fails and cardiovascular and autonomic collapse ensue. Hypoxemia, hypotension, and cerebral edema develop, which only worsen neuronal and organ damage (8). Clinically and electrographically, GCSE begins with discrete electroclinical seizures that quickly evolve into continuous seizure activity. After several minutes, motor activity will abate but persistent electrographic seizures will continue. Frequent well-developed or continuous electrographic seizures then degenerate into a waxing–waning pattern of ictal discharges. The EEG further devolves into continuous epileptiform discharges with brief periods of background suppression. As the periods of background suppression increase in length, continuous epileptiform activity gives way to periodic discharges on a very low amplitude background (9).

An interesting aspect of the natural history of SE is the tendency for it to become self-sustaining. This is an important concept that is critical to understand, so that effective treatment is initiated rapidly. Though many cases of status epilepticus will self-terminate, the risk of self-perpetuating SE becomes more important when considering the pharmacoresistance that can develop. Many of the commonly used drugs to stop status will lose effectiveness rapidly, especially GABAergic agents like benzodiazepines and even some antiepileptic drugs (AEDs) such as phenytoin (7).

### Systemic Complications

It is critical to understand that GCSE is a systemic process that can result in multiorgan failure. At the onset of SE, there is a massive surge of sympathetic activity originating from the brain. This wave of autonomic activity will drive extreme tachycardia and hypertension causing cardiac injury, arrhythmias, as well as neurogenic pulmonary edema

and hypoxia. As a result of the convulsive activity, there is a risk of airway compromise and aspiration of gastric contents. Clinical seizure activity also results in massive muscle contraction with rhabdomyolysis, metabolic acidosis, and hyperpyrexia. Rhabdomyolysis results in renal injury or failure, which will further worsen the metabolic acidosis and increase the likelihood significant metabolic abnormalities. Hyperpyrexia can worsen neuronal injury and metabolic acidosis can further compromise the cardiovascular system. After several minutes of clinical seizure activity, the sympathetic surge will give way to autonomic collapse with hypotension and loss of respiratory drive. If untreated, further organ damage or failure will ensue.

### Neuronal Injury

Neuronal damage likely results from a combination of systemic complications as well as intrinsic injury produced by persistent neuronal hyperactivity. Animal and human studies show elevation in markers of neuronal injury after nonconvulsive seizures (NCS) and SE, including elevated neuronal-specific enolase levels and hippocampal atrophy (10,11). A small but increasing pool of evidence from critically ill populations has shown that electrographic seizure activity contributes to secondary brain injury or worsening neuronal damage (12).

### Treatment

It is imperative that there be no delay in treating GCSE. In a landmark prehospital GCSE trial conducted by the VA Cooperative Study Group, 2 mg to 4 mg of intravenous (IV) lorazepam was found to be successful in terminating SE in 60% of patients when compared to diazepam or placebo (13). In a follow-up trial, lorazepam was found to be effective in stopping nearly 65% of GCSE cases when compared to diazepam, phenytoin, and phenobarbital (14). Because of this work, prehospital benzodiazepine administration is now the standard of care for patients with GCSE. A more recent and equally important trial has shown the effectiveness and superiority of 10 mg of intramuscular (IM) midazolam over IV lorazepam (15). Though the effect is likely due to the ease of administration of an IM injection, this trial provides additional therapeutic options. Other therapies that are available for patients in GCSE include intranasal and buccal midazolam and rectal diazepam. Though not all of these are approved in the United States, they are important therapeutic alternatives.

Similar to the prehospital setting, parenteral benzodiazepines remain the first-line drugs for treating GCSE emergently in the hospital (Table 34.1). Second-line therapy with AEDs is generally required after a benzodiazepine has been administered. Most hospitals have individual protocols for treating GCSE (Figure 34.1). Though protocols differ between institutions, phenytoin is probably used most often, followed by valproic acid. These drugs will likely remain AEDs of choice given IV formulation, physician

TABLE 34.1 Agents Used to Treat Status Epilepticus

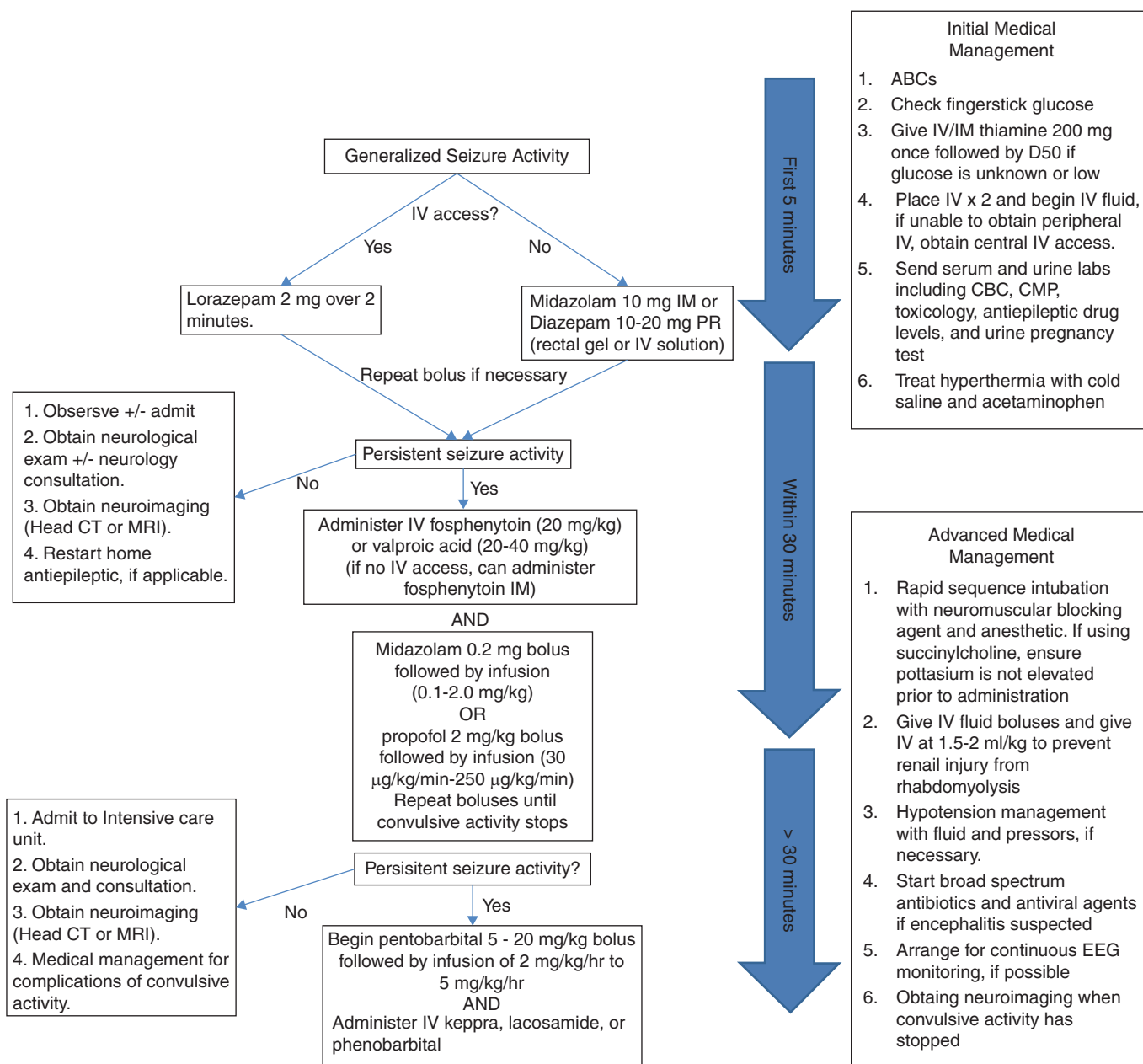
DRUG	LOADING DOSE	MAINTENANCE DOSE	MECHANISM OF ACTION	METABOLISM	ADVERSE REACTION
<b>First-Line Agents</b>					
Lorazepam	0.1 mg/kg up to 4 mg administered at <2 mg/min IV	None	GABA agonist	Hepatic	Sedation and respiratory depression
Midazolam	0.2 mg/kg IV/IM up to 10 mg IM	None	GABA agonist	Hepatic with active metabolite cleared renally	Sedation and respiratory depression
Diazepam	0.1 mg/kg IV up to 10 mg OR 0.2 mg/kg up to 20 mg rectally	None	GABA Agonist	Hepatic	Sedation and respiratory depression
<b>Second Line Agents</b>					
Fosphenytoin	15–20 mg/kg IV up to 150 mg/min	5–8 mg/kg IV/PO/NG divided every 8 to 12 hours	Sodium channel modulator	Hepatic/cytochrome enzyme induction	Hypotension, arrhythmia, cardiovascular depression
Phenytoin	15–20 mg/kg IV up to 50 mg/min	5–8 mg/kg IV/PO/NG divided every 8 to 12 hours	Sodium channel modulator	Hepatic/cytochrome enzyme induction	Hypotension, arrhythmia, cardiovascular depression, infusion site reaction
Valproic Acid	20–40 mg/kg IV up to 6 mg/kg/min	30–60 mg/kg/day divided every 6 hours	Multiple mechanisms including glutamate/ NMDA inhibitor and sodium channel modulation	Hepatic/cytochrome enzyme inhibition	Mild somnolence, thrombocytopenia, hyperammonemia, pancreatitis
<b>General Anesthetics</b>					
Midazolam	0.2 mg/kg boluses prior to starting infusion. Additional boluses every 10 minutes until seizures stop up to 2 mg/kg	0.1 mg/kg/hr to 2 mg/kg/hr continuous Infusion	GABA agonist	Hepatic with active metabolite cleared renally	Cardiorespiratory depression, hypotension
Propofol	2 mg/kg boluses	2–15 mg/kg/hr	GABA agonist	Hepatic	Propofol infusion syndrome with metabolic acidosis, Avoid prolonged high-dose infusion >5 mg/kg/hr to 48 hrs
Pentobarbital	20 mg/kg loading dose	1 mg/kg/hr up to 5 mg/kg/hr	GABA potentiation	Hepatic metabolism/enzyme induction	Cardiorespiratory depression, hypothermia, immune suppression

(continued)



TABLE 34.1 Agents Used to Treat Status Epilepticus (*continued*)

DRUG	LOADING DOSE	MAINTENANCE DOSE	MECHANISM OF ACTION	METABOLISM	ADVERSE REACTION
<b>Third Line Agents</b>					
Levetiracetam	20 mg/kg or 1,500–4,500 mg IV up to 500 mg/min	2,000–4,500 mg per day divided every 8 hours.	Unknown; Binds to Synaptic vesicle protein 2A	Renal with minimal hepatic clearance/no enzyme induction	No significant reactions acutely
Lacosamide	400 mg IV over 5 minutes	400 to 600 mg/day divided every 12 hours	Sodium channel modulation	Hepatic and renal clearance/no enzyme induction	Possible PR interval prolongation
Phenobarbital	20 mg/kg IV up to 60 mg/min	1–4 mg/kg/day divided every 6 to 8 hours	GABA potentiation	Predominantly hepatic with some renal clearance/ prominent hepatic enzyme induction	Sedation, hypotension, cardiovascular depression
<b>Oral Agents</b>					
Topiramate	100 mg every 12 hours	200 mg up to 1,600 mg divided twice per day	Multiple mechanisms including sodium channel modulation, GABA potentiation, carbonic anhydrase inhibition, and glutamate/ $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) inhibition,	Predominantly renal with some hepatic metabolism/possible enzyme induction at high dose.	Metabolic acidosis
Pregabalin	75 mg every 12 hours	150 mg up to 600 mg divided 3 times a day	Calcium channel modulation	Renal	No significant adverse effects
Gabapentin	300 mg every 8 hours	900 to 3,600 mg/day divided every 6–8 hours	Calcium channel modulation	Renal	No significant adverse effects
Felbamate	400 mg every 8 hours	1,200 mg every 8 hours	GABA potentiation and glutamate/NMDA inhibition	Hepatic and renal	Aplastic anemia and hepatic failure
<b>Other infusions</b>					
Ketamine	1.5 mg/kg IV up to 4.5 mg/kg every 5 minutes until seizures controlled	1.5 to 7.5 mg/kg/hr continuous infusion	Glutamate/NMDA inhibition	Hepatic	Hypertension, increased intracranial pressure
Lidocaine	1–5 mg/kg IV every 5 minutes until seizures controlled	Up to 6 mg/kg/hr continuous infusion	Sodium channel modulation	Hepatic	Arrhythmia



**FIGURE 34.1** Example of GCSE protocol.

comfort with dosing and side effects, and a belief in efficacy. However, there are little data regarding differential efficacy of phenytoin, valproic acid, and other AEDs. Fosphenytoin, a prodrug of phenytoin, can be an easily and rapidly administered IV with fewer of the side effects seen with intravenous phenytoin, namely, hypotension, and without the risk of soft tissue necrosis and “purple glove syndrome” in case of peripheral extravasation. Valproic acid is likely as effective as phenytoin and can be administered with minimal sedation, cardiac, and respiratory side effects. However, it should be avoided in those with known or suspected metabolic disorders and children under the age of 2 due to the risk of hepatotoxicity. Owing to uncommon instances

of significant thrombocytopenia and rare bleeding complications, it may be wise to avoid in patients who have a bleeding diathesis or will require neurosurgery. Phenobarbital, once used quite often, has lost favor in recent years due to adverse effects, including prolonged sedation and hypotension, especially when administered in large doses. Its use is now limited to cases of refractory status epilepticus. Other agents such as levetiracetam and lacosamide will likely supplant older drugs in the future as they are now used frequently in the hospital and are gaining popularity due to their ease of administration, dosing, and benign side effect profiles. However, they are presently used as third- or fourth-line agents in most cases.

## Diagnostic Tools

Diagnostic neuroimaging will be necessary for all patients with new-onset SE and for most others, unless there is a clear explanation like medical noncompliance. However, neuroimaging, like emergent head CT, should not delay treatment. For patients with new-onset seizures and SE, brain MRI with contrast would be the imaging modality of choice. It is superior to CT for diagnosing conditions that are likely to cause SE, including encephalitis. MRI is more suitable for diagnosing very focal lesions, including those that cause FSE. MRI findings caused by SE can sometimes be seen after prolonged seizures, including T2 and restricted diffusion changes in the thalamus, cortical gray matter, and corpus callosum. These changes can be mistaken for stroke or encephalitis but likely indicate neuronal distress or injury as a result of continuous seizure activity. These changes are reversible in most patients with SE. In cases of RSE or SRSE, other imaging may be necessary such as PET or SPECT to precisely localize a seizure focus or determine whether a complex electrographic activity represents an ictal EEG pattern.

cEEG monitoring is critical in the management of SE. Given the high incidence of NCSE after GCSE and the potential for further neuronal injury from persistent seizure activity, adequate monitoring for nonconvulsive seizure activity is essential. Recent guidelines from two critical care organizations endorse cEEG monitoring as part of the management strategy for GCSE (2,16). If the patient remains comatose after convulsions have ceased, the patient should be monitored for 48 hours in most cases. If nonconvulsive seizures are found, cEEG monitoring should continue for at least 24 to 48 hours after seizures are terminated.

## REFRACTORY AND SUPER REFRACTORY STATUS EPILEPTICUS

RSE can be generally defined as SE that has not responded to first- or second-line therapies. In the vast majority of RSE, the next agent of choice will be a general anesthetic such as midazolam, propofol, or pentobarbital. There are institutional preferences for the choice of anesthetic but all three are likely equivalent in definitively treating SE. Each agent has unique side effects that may limit usage in different patients. Midazolam, a short-acting benzodiazepine, should be bolused and an infusion started at a relatively high dose (0.5 mg/kg/hr to 2 mg/kg/hr) until seizures have stopped. However, high doses of midazolam are associated with hypotension and respiratory depression typically requiring mechanical ventilation. Though it is short acting in small doses, prolonged infusions of midazolam may result in profound sedation for hours or even days after the infusion is stopped. Propofol, a potent GABA agonist dissolved in a lipid emulsion, is likely as effective as midazolam and has similar effects on vasomotor tone and respiratory drive. In uncommon circumstances, particularly in very young patients, high dose, prolonged propofol infusion can result in propofol infusion

syndrome (PRIS). PRIS is a dangerous condition associated with rhabdomyolysis, metabolic acidosis, and profound bradycardia. Prolonged infusions can also lead to significant hypertriglyceridemia, putting the patient at risk of pancreatitis in rare circumstances. Monitoring triglyceride levels is often wise when infusing propofol for an extended period. Pentobarbital, also a potent GABA agonist, is often used in RSE. It will stop virtually all seizure activity but likely has an equal risk of seizure recurrence after it is discontinued. Unlike midazolam and propofol, pentobarbital has a very long half-life and even relatively short duration infusions will result in prolonged sedation. It is a potent vasodilatory agent and virtually all patients require support with a vasopressor agent. Pentobarbital is also thought to be an immune suppressant and may put the patient at further risk of developing an infection, particularly aspiration pneumonia. Anecdotally, patients that are placed on pentobarbital infusions often develop hypothermia as well as gastric ileus as a result of the infusion, as well other critical illness comorbidities. Both conditions can make caring for such patients very challenging. Initial titration of these drugs should be directed at terminating convulsive and subsequent nonconvulsive SE as quickly as possible. Once the seizures are terminated, it is common practice to slowly taper these agents and observe for recurrence of seizure activity. Each dose reduction should be performed incrementally every 8 to 12 hours in most cases with frequent monitoring by cEEG. Unfortunately, it is quite common for seizures to recur when decreasing the dose of the infusion. If this occurs, the infusion should be increased back to the prior level and consideration should be given to adding an additional AED based on physician preference or hospital protocol.

The use of oral AEDs does not appear to have a role in the early treatment of status epilepticus, except to resume a patient's home medicine when no IV formulation is available (ie, carbamazepine). Oral medications may have some role in treating RSE and SRSE if other IV agents have failed or are contraindicated. This may be important if an AED with no IV equivalent is desired. For example, adding pregabalin to levetiracetam and phenytoin as a fourth-line agent. However, oral medications must be used with caution as gastric absorption in the critically ill is not guaranteed.

In cases of SRSE, other IV infusions can be used, including ketamine, lidocaine, and magnesium. Ketamine is an NMDA receptor antagonist that, unlike other IV infusions, can cause hypertension and may increase cerebral blood flow and intracranial pressure. Lidocaine is a sodium channel modulator that may also have a role in some cases of SE. Magnesium has been used for many years as an adjunctive treatment for RSE and is safe in most patients. Other agents used to treat SE in rare circumstances include volatile anesthetics such as isoflurane. Similarly, mild therapeutic hypothermia and urgent resective surgery can be considered for SRSE if there is a clear focus of seizure onset. Though the level of evidence to support such treatments is limited to case studies and small case series, it is worthwhile to consider these agents in special circumstances (1).

With the recognition of NORSE and other causes of SRSE, immune and anti-inflammatory therapy may have a role in treatment (6). Such therapies include pulse steroids, ACTH, intravenous immunoglobulin (IVIG), and plasmapheresis. Similarly, steroid-sparing immunotherapy such as rituximab or cyclophosphamide can be used if a specific etiology is determined to be the cause or associated factor in SRSE.

### COMPLEX PARTIAL STATUS EPILEPTICUS

CPSE is a state of recurrent or continuous seizure activity that manifests with some alteration in awareness or memory but without obtundation or coma and without overt convulsive activity. It was once thought to be rare diagnosis but is likely more common particularly with widespread usage of cEEG monitoring. Similar to GCSE, the state of the patient is likely related to the phase of CPSE that the patient is experiencing and can vary from recurrent complex partial seizures to a continuous period of stupor or twilight state of confusion or psychotic behavior. Patients may cycle between these different states if left untreated. Establishing the diagnosis of CPSE versus spike-wave stupor from generalized epilepsy may be difficult and should be based on historical and clinical characteristics of the patient. Although this represents a form of NCSE, it is likely different from NCS experienced by critically patients. The impacts of CPSE and long-term neuronal damage are unclear (17).

### NONCONVULSIVE SEIZURES AND NONCONVULSIVE STATUS EPILEPTICUS IN CRITICALLY ILL PATIENTS

NCS and NCSE have been recognized phenomena for decades, but their prevalence in the ICU and impact on patient outcomes has only recently been discovered. Numerous studies in the past 15 years have consistently noted a relatively high rate of NCS and NCSE in the ICU. The rates of NCS and NCSE vary between studies but are noted in 15% to 30% and 10% to 15%, respectively, depending on the population studied (16). The incidence of NCS is particularly high after the cessation of GCSE and may be present in 30% or more of patients (14). As with GCSE, a history of seizures or epilepsy is a significant risk factor for developing NCS and NCSE. RSE, when detected, requires cEEG monitoring in order to guide titration of AEDs and sedative medications (2). However, many ICU patients with NCS never have definitive clinical evidence of seizure activity before developing NCS. In one study that examined 570 patients monitored for detection NCS, over 90% of those with subclinical seizures never had a clinical seizure (18). Subtle clinical evidence (unexplained eye movements or twitching) of seizures may be present but is not a consistent or accurate indicator of NCS (19). Numerous predictors of NCS in obtunded or comatose

ICU patients have been found, but the most consistent predictors include a history of epilepsy, CNS infection, brain tumors, neurosurgical procedure, traumatic brain injury, and intracranial hemorrhage, including lobar and deep intraparenchymal and subarachnoid bleeds. Populations in the NeuroICU appear to be at the greatest risk with a few exceptions. Intracranial hemorrhage is a very common condition seen in the NeuroICU and can have significant morbidity and mortality associated with it, depending on the type of hemorrhage. Intracerebral hemorrhage is a risk factor for acute and chronic seizures, particularly if the hemorrhage is cortical or if it results from an arteriovenous malformation. Cerebral sinus venous thrombosis with hemorrhagic infarction is also associated with a high rate of seizures. Seizures in this population are associated with increased midline shift on CT and a larger hematoma volume (20). Subarachnoid hemorrhage is a very unique form of intracranial hemorrhage associated with significant morbidity and mortality due to the occurrence of cerebral vasospasm and delayed cerebral ischemia. NCS may occur in nearly 20% of patients with over half of those cases being NCSE. Severe traumatic brain injury is similarly associated with a significant risk for NCS, particularly in those with large cerebral contusions, depressed skull fractures, and other penetrating injuries. Although of slightly lower risk than other forms of brain injury, central nervous system (CNS) infections including meningitis and encephalitis are associated NCS in 13% of patients. The occurrence of subclinical seizures and periodic epileptiform discharges is associated with increased mortality in this population (16).

In general medical ICUs, NCS also appear to be common. cEEG monitoring has become an integral part of the care pathway in patients who have experienced cardiac arrest and are undergoing therapeutic hypothermia. Monitoring of these patients reveals an incidence of NCS in up to 30%. Though the rates appear to be lower, patients without primary brain injury with an unexplained change in level of consciousness, particularly coma, are at risk for having NCS. In medical ICU patients with no history of brain injury, 10% may have electrographic seizures with the main predictor of NCS being sepsis. A convulsion before cEEG monitoring increases the risk but severe sepsis, hepatic, or renal dysfunction remain the most significant predictors. Recent recommendations from the European Society of Intensive Care Medicine recommend cEEG monitoring in those with severe sepsis or metabolic encephalopathy who are comatose (16).

Studies in comatose children have found an equal and in some cases a higher percentage of electrographic seizures than in adults. Risk factors of NCS are similar to that of the adult population and include altered mentation with a known neurologic condition, including cardiac arrest, TBI, and other structural neurologic conditions. Similarly, children with prior GCSE or recent seizures are at the greatest risk. Specialized populations without prior neurologic injury also appear to be at risk, particularly those undergoing



surgery for congenital heart disease. The risk is likely lower than those with known neurologic disease (21).

Although NCS and NCSE are common in the ICU, the effect of these seizures on patient outcomes is less clear. The preponderance of evidence seems to suggest that subclinical seizures are associated with neuronal injury and metabolic distress in the brain. Neuron-specific enolase levels are elevated in patients with NCS as they are in other conditions associated with brain injury (10). In patients with cerebral microdialysis catheters, seizures are associated with increased markers of metabolic distress, namely increased lactate:pyruvate ratios and glutamate levels (22). Studies looking at identification and treatment of NCS found that seizure duration and time to diagnosis may have inverse relationship with good outcome. The occurrence of NCS in critically ill children is associated with worse neurodevelopmental outcome and mortality (23). In some conditions in adults such as subarachnoid hemorrhage, sepsis, and CNS infections, it is clear that NCS are associated with a worse outcome. However, significant clinical evidence indicating worse outcome is lacking in many adult patients where NCS are found, including ischemic stroke and intracerebral hemorrhage. In others such as adults with TBI, the data are less clear. There are suggestions including the finding of increased hippocampal atrophy after subclinical seizures in TBI. One study found improvements in outcome before and after cEEG introduction. For victims of cardiac arrest, it appears that NCSE early in the clinical course is associated with poor outcome, particularly during hypothermia while under sedation. For those not undergoing therapeutic hyperthermia (TH), NCSE is generally associated with a poor outcome. It is unclear if aggressive treatment of these seizures will have any effect on outcomes in patients (16).

Owing to the lack of definitive outcome data in some patient populations, some argue that NCS are epiphenomena of critical illness and do not justify aggressive treatment in many cases. These concerns are not unfounded as high-dose sedative administration such as pentobarbital and midazolam can be associated with multiple medical complications. However, it is unlikely that these treatments adversely affect outcome and that any effect seen on morbidity and mortality is related more to baseline illness or to seizure control. In cases of RSE, which will be nonconvulsive almost by definition, aggressive treatment is a necessity. Early detection and early treatment of NCS after RSE is imperative. In patients whose sole manifestation of NCS or NCSE is that of coma or altered mental status, there is no consensus on a treatment approach. Arguments for aggressive treatment are based on the finding of increased mortality in certain populations and the findings of worse outcome in those in whom the diagnosis had been delayed. Special consideration should also be taken when choosing which agents to administer to these patients. Administration of certain anticonvulsants like phenytoin is associated with worse neurocognitive and motor outcomes in select patient populations.

There are many types of SE. While many types of SE are obvious clinically, many are not and are recognized only with cEEG monitoring. GCSE is associated with significant postictal morbidity. SE in critically ill subjects is common, with up to 20% of those undergoing cEEG monitoring have such seizures. Treatment consists of prehospital and in-hospital therapy. Though there is a paucity of data on the comparative effectiveness of various AEDs, in general, treatment with a benzodiazepine is followed by an AED like levetiracetam or phenytoin. If seizures continue (RSE), other nonsedating medications or intubation with aggressive management is appropriate. Studies are being planned and conducted that will evaluate the efficacy of treatment of various new and novel compounds.

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# Reproductive Issues

*Lynn Liu*

## HISTORY

Historically, people with epilepsy (PWE) around the world have been stigmatized due to misconceptions about seizures. In ancient times they were typically thought to be possessed by evil spirits and therefore were feared. The belief that seizures were contagious resulted in isolation from the rest of society. PWE were also legally denied the right to go to public places such as restaurants, theaters, or other recreational areas. Based upon these misconceptions, the 17th-century treatment for women with epilepsy (WWE) included hysterectomies. Laws were established over two hundred years ago that PWE could not marry or procreate. In 1956, 17 states in the United States still prohibited PWE from marrying, and it was not until 1980 that the last state repealed this law. During the same time period, laws enforcing eugenic sterilization for PWE existed; the last state repealed this law in 1970 (1). As a result, the issue of reproduction for PWE is a fairly modern concept.

Even with progress to the legal system, social awareness and acceptance of comorbid mental health disorders and improved treatment for epilepsy, the physiologic barriers to reproduction persist at various levels, including the epilepsy syndrome itself, hormones, and medications. PWE feel isolated and have limited interactions with other people. In general, they have reduced quality of life (QOL), which diminishes their desire to have intimate relationships and even consider having children. Epilepsy syndromes that start earlier in life impact social and physiological development compared with adults-onset epilepsy. Both men and women with epilepsy have more endocrine dysfunction compared to the general population and as a result have reduced libido and fertility. The medications they take to control their seizures further alter mood, seizure frequency, hormones, or interact with other medications. Women with epilepsy have additional fears. Family planning and choosing the appropriate contraceptive methods are topics they feel providers try to avoid. They worry about their children inheriting their epilepsy, the effect of their medications on a developing fetus, and the additional concerns about undergoing a pregnancy and delivery. Supports and precautions should be considered for the mother with epilepsy raising

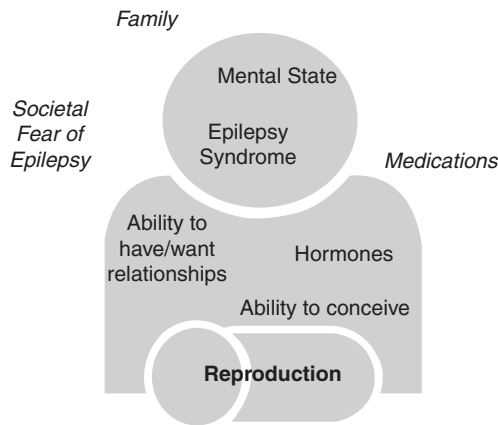
children. Misinformation in the medical community and society persist even in the face of established practice parameters for the management of WWE and public campaigns. This chapter reviews some of the issues related to reproduction in men and women with epilepsy.

## RELATIONSHIPS

In order for anyone to develop a successful relationship, they need positive self-esteem and have an appropriate mental state with adequate social supports. PWE have higher rates of both depression and anxiety compared to the general population in part due to the unpredictable nature of seizures and the limitations society sets on PWE. Physiological consequences of seizures, both generalized and focal, along with their treatments alter the neurologic circuitry of mood and behavior. Psychosocial factors that restrict PWE from having meaningful relationships include reduced independence and lower socioeconomic status. Both factors sustain the cycle of limited social interaction and isolation (Figure 35.1).

## Mood Disorders

Depression and anxiety have been estimated to affect 30% to 50% of PWE; a higher rate compared with the general population, which ranges from 7.2% to 20% in the literature (2). The wide range of percentages depends on whether the population studied was based on community or tertiary care centers where the epilepsy syndrome may be more difficult to control. Their risk of suicide is estimated to be 10-fold over the general population especially if they feel hopeless (2). Theories why PWE may be more vulnerable to depression arise from the unpredictable nature of an uncontrollable adverse event: the seizure. This results in a poor health-related locus of control and learned helplessness. With this, they tend to have lower self-esteem. They use primitive coping mechanisms such as escape-avoidant and wish-fulfilling fantasy. Mental health providers unfamiliar with the diagnosis of epilepsy have concerns that starting antidepressant medications will increase the likelihood of a seizure, and as a result, many PWE suffering from depression are undertreated.



**FIGURE 35.1** Pictorial representation of how epilepsy does not effect the individual alone, but it also affects the way they feel about themselves and their interactions with family and society.

### Epilepsy Syndrome and Mood

The type of seizure influences the rates of depression and anxiety both positively and negatively. The diffuse discharge of generalized seizures can exert an effect on depression much like electroconvulsive therapy, and with improved seizure control, increased mood issues can emerge. Focal seizures, particularly seizures arising from the temporal region, activate the limbic system. Amygdalar seizures initially get misdiagnosed as panic attacks because they are characterized by episodic fear, especially if they do not progress to confusion and staring, indicating an evolution to the complex phase of a seizure. Episodic stimulation of the limbic circuitry has been associated with both elevated and depressed mood, both pre- and postictally. Within the frontal lobe, seizures arising from the cingulate gyrus activate in the limbic system as well. Prefrontal cortex seizures have been associated with altered behavioral regulation. Knowing the localization of the seizure can provide further understanding to the management of the patient's overall well-being.

Most of the medications used to treat seizures have common side effects of sedation, fatigue, and anhedonia. Nonetheless, seizure medications have been noted specifically to alter mood beyond the improved control of seizures. Mental health providers use seizure medications to stabilize mood disorders independent of the diagnosis of seizures.

### Psychosocial Factors

PWE tend to have lower academic achievement, lower financial status, and limited transportation. Furthermore, PWE are less likely to have friends, steady relationships, or marriage. If their epilepsy begins while they are still in school, the seizure frequency and medications impact their educational experience. Lower educational status, limited transportation, work restrictions, and increased absenteeism all result in less employment. They remain dependent on their families for support. If they marry, the person with

epilepsy takes on the dependent role in the relationship and feels limited in their independence. However, it has been observed that after successful surgery for medically intractable epilepsy, improved seizure control leads to a change in marital dynamic, often leading to divorce due to increased independence for the person with epilepsy.

Although culturally specific, surveys worldwide suggest that PWE are less likely to marry and more likely to divorce compared to the general population. The stability of the marriage typically has been associated with later age of onset of the epilepsy and better seizure control. The decrease in marriage rates cannot be explained by the increased rates of developmental delays and cognitive impairment completely. PWE discuss whether to disclose the diagnosis before marriage; most do not. In Canada, marriage rate were estimated to be 59% of expected in men with epilepsy and 83% of expected in women especially if the epilepsy began before the age of 20 (3). In a study conducted in India, one of the last countries to repeal the marriage laws, the rates were even lower: 46.6% in men and 46.7% in women (3). In an opinion survey about marriage and raising children, people in Hong Kong agreed that PWE should be able to marry and have children, but they would discourage their children from marrying someone with epilepsy (3).

### SEXUALITY

Once a person with epilepsy commits to an intimate relationship, about one- to two-thirds encounter higher rates of sexual dysfunction. The majority experience hyposexuality with decreased libido, which is the desire or interest in sexual activity, and diminished potency, which is the physiologic arousal that occurs during sexual activity. In men, these changes are externally evident as decreased penile rigidity and tumescence. A medical evaluation should clarify if the altered responses are a result of a mood disorder or a physiological disorder. The presence of nocturnal erections during rapid eye movement sleep indicates normal physiology and distinguishes the cause of decreased potency to be related to emotional issues. WWE report that they do not experience orgasms and have increased dyspareunia, vaginismus, and reduced vaginal lubrication with sexual intercourse. Both men and women with epilepsy have reduced blood flow to genital tissues in response to visual erotic stimuli compared to age-matched controls.

### Epilepsy Syndrome and Sexuality

Some associate intimacy with fear because hyperventilation and physical exertion may result in a seizure. Others who have sexual auras have negative associations with seizures. Automatisms of a sexual nature such as masturbation or removing clothing postictally have been interpreted as hypersexuality or paraphilias historically in the literature. The advent of video EEG (vEEG) monitoring documenting the simultaneous electrographic pattern documents the ictal nature of these acts. Repeated stimulation of the limbic



system by seizures can alter sexuality. Bilateral mesial temporal injury is associated with Kluver-Bucy syndrome.

The cause of altered sexuality has a complicated network of etiologies related to hormones, medications, and seizures. PWE have reduced levels of sex steroids especially testosterone and estrogen, which are necessary for both men and women in appropriate amounts for maturation, sexual desire, and reproductive fitness. Seizure medications, especially those that induce hepatic enzymes, reduce the bioavailability of these sex hormones. Seizure types can change the regulation of hormonal secretion perpetuating the cycle.

### Medications and Sexuality

Starting in the 1970s to 1980s, researchers observed that the use of seizure medications influenced the reproductive endocrine system, resulting in reduced sexual function (4). Both gonadal hormones and many seizure medications are metabolized through the cytochrome P450 (CYP450) and specifically the 3A4 isoenzyme. When agents such as phenytoin, carbamazepine, phenobarbital, and primidone (PRM) are used, a couple of things happen concomitantly: increased metabolism of the sex hormones and an increased production of sex hormone binding globulin (SHBG). This protein binds circulating sex steroids to make the free fraction less bioavailable and not available to act on the appropriate end organ. The total levels may still be within the normal range, but the free level will be lower. Not only are estrogen and testosterone levels affected, so are dehydroepiandrosterone (DHEAS), a precursor to both androgens and estrogens. As a result of the lower active hormone levels, pituitary feedback also diminishes.

In contrast, valproic acid (VPA) inhibits hepatic enzymes and yet it also has been associated with sexual dysfunction in both men and women with epilepsy. The mechanism studied in the 1990s in WWE who also have menstrual dysfunction suggest an increased rate of polycystic ovarian syndrome (PCOS). This syndrome is evident if the use of VPA began earlier than 20 years and for those who gain weight. VPA changes androgen levels before puberty and therefore could influence maturation in young girls.

Medications that do not influence the CYP450 system significantly do not cause as many hormonal changes. Oxcarbazepine at low doses is not considered an enzyme inducer, but at higher doses it can induce CYP450. Switching from carbamazepine to low-dose oxcarbazepine can reverse some of the endocrine dysfunction, but its effect on reproductive hormones is dose related. Lamotrigine has not been shown to alter the reproductive endocrine system in contrast to animal studies. In fact, switching to lamotrigine from VPA seems to reverse some of the observed endocrine dysfunction in both testosterone and insulin within a year of changing medications. Data are limited on the newer medications and none of the other seizure medications have been rigorously studied in this same manner.

### Hormones and Sexuality

In addition to their reproductive functions, gonadal sex steroids also have neuroactive properties. Estrogen in animal models stimulates glutamate and inhibits gamma-aminobutyric acid (GABA) receptors. It has also been demonstrated to alter neuronal architecture and increase the number of dendritic spines. All these changes can lead to a proconvulsant state. In contrast, progesterone inhibits glutamate and stimulates GABA, resulting in a relatively protective state. The actions of testosterone on seizures are not clear. Animal models and human tissue samples also note an upregulation of androgen receptors in the presence of enzyme-inducing medications and therefore increased sensitivity to neuroactive steroids. Aromatase (CYP19), another CYP450 enzyme, converts androgens to estrogen and acts on the cerebral cortex. Several seizure medications can inhibit its actions and reduce the conversion of testosterone to estrogens; the end result is an increase in testosterone and less estrogen levels in women.

The brain regulates the hypothalamic–pituitary–gonadal axis with regular pulsatile stimulation to the hypothalamus. Pituitary hormones are necessary for normal sexual function. Synchronized discharges of generalized seizures disrupt the regulation by causing a surge in prolactin levels within 20 minutes of the seizure. In animal models, temporal lobe seizures and interictal epileptiform discharges also alter the regular pulsatile stimulation of the hypothalamus, which in turn also increases prolactin secretion. One function of prolactin is to provide sexual gratification by inhibiting dopamine released during sexual intercourse. Chronic hyperprolactinemia has been associated with hyposexuality.

Owing to the personal nature of sexuality, providers rarely ask or discuss the topic despite the implications to quality of life. In men with erectile dysfunction, evaluation for alternative causes such as cardiovascular disease, diabetes, or depression should be initiated or opt for treatment with phosphodiesterase type 5 (PDE5) inhibitor such as sildenafil. In the evaluation and treatment of women, just as in men, it is important to explore whether the sexual dysfunction is related to emotional well-being or physiological changes. The treatment of hyposexuality in women has not been well studied and there are few recommendations other than sex therapy and lubrication. Working with a reproductive endocrinologist and replacing necessary hormones can also be of benefit.

### FERTILITY

Fertility rates have been noted to be lower for both men and women with epilepsy compared to their sibling controls. Fertility in married WWE is 69% to 85% expected number of offspring especially those who have temporal lobe epilepsy (5). WWE have an increased frequency of menstrual dysfunction. Men with generalized epilepsy have 36% fertility rate of their siblings. Men with epilepsy have decreased

sperm counts with abnormal morphology and impaired motility. Hypogonadism can be related to low testosterone levels due to reduced gonadotropin-releasing hormone (GnRH). Hyperprolactin states can result in reduced reproductive function. There may be cultural influences as well, since in Iceland there are no noted changes in fertility. Factors that seem to influence fertility are localization-related epilepsy, especially early age of onset, hormonal regulation, and medications used to treat seizures.

### **Epilepsy Syndrome and Fertility**

Menstrual disorders in WWE are more frequent in women who have more seizures. The characteristics of the menstrual dysfunction may have lateralized differences. Left temporal lobe seizures increase GnRH release, which results in increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) that can cause altered follicular development in the ovaries and increasing testosterone levels in women as a potential mechanism for polycystic ovarian syndrome (PCOS). In contrast, right temporal lobe seizures results in decreased GnRH and thus LH and FSH resulting in lower estrogen levels and increased prolactin levels. The clinical consequence results in hypothalamic amenorrhea and possibly premature menopause that begins before 30 years of age.

### **Medications and Fertility**

Epilepsy and the use of VPA both have been independently associated with PCOS. Studies have demonstrated increased rates of PCOS in WWE. On further evaluation, it was suggested that this syndrome was more frequently associated with left temporal lobe epilepsy and the use of VPA in contrast to the use of lamotrigine. The frequency of PCOS in WWE was estimated between 10% and 20% versus 5% and 6% in the general population (6). Recently this association has been called into question because of different study designs and different definitions of polycystic ovaries (PCO) and PCOS. PCO have more than 10 follicular cysts sized between 2 and 8 mm that are located in the periphery of the ovaries and have increased ovarian stroma or size. This finding can be identified by ultrasound in the setting of menstrual irregularity due to erratic or infrequent ovulation. PCOS defined by an NIH consensus statement includes ovarian dysfunction and hyperandrogenism or hyperandrogenemia exclusive of other endocrine abnormalities. Clinical manifestations include menstrual dysfunction, infertility, hirsutism, and obesity with hyperinsulinemia. Three hypothetical mechanisms include (a) increased LH pulse frequency and amplitude, resulting in retained follicular cysts and continued androgen production that is not converted to estrogens by aromatases, (b) primarily ovarian failure, and (c) reduced sensitivity to insulin (6).

### **Hormones and Fertility**

The relationship between sex steroid hormones and seizures has been well established since Gowers. Some women

observe that their seizures vary in frequency based on the phase of their menstrual cycle: catamenial epilepsy. On evaluation, WWE tend to be most vulnerable when the estrogen/progesterone ratio is higher. Studies of this phenomenon categorize vulnerable timeframes into three periods identified as C1, C2, and C3. Two timeframes of ovulatory cycles as progesterone levels are falling rapidly include peri-ovulation (C1) when there is an LH surge and a rise in estrogen levels while progesterone levels remain low and peri-menstrually (C2) (7). For a variety of reasons WWE have a lower proportion of ovulatory cycles and a higher proportion of anovulatory cycles compared to their sibling controls. The vulnerable time frame for seizures during an anovulatory cycle, when there is an inadequate luteal phase, ranges from ovulation to the onset of menses (C3). In order to establish the diagnosis, a woman should maintain both a seizure diary and a menstrual calendar and chart the relationship between the two for at least three cycles. They can monitor which cycles are ovulatory and which are not with over-the-counter ovulation kits. Sharing this information with her provider may open discussions in treatment options.

### **CONTRACEPTION**

Women use hormonal agents for a variety of indications: family planning, dysfunctional uterine bleeding, and menstrual cycle regulation. Hormonal preparations come in a variety of forms including pills, patches, and hormonally impregnated devices. This decision to choose an effective and tolerable method in a woman with epilepsy has added considerations including the effect of hormones on seizure control, the effect of seizure medications on hormonal contraceptives, and the effects of hormonal contraceptives on seizure medications. With the variety of types and forms available, the decision may need to be coordinated with a primary care provider or gynecologist.

The majority of oral contraceptive preparations are composed of a combination of an estrogen and a progestin. The estrogen component is the synthetic agent, ethinyl estradiol (EE), and the dose can vary by preparation. Maintaining steady levels of EE inhibits the LH surge necessary for ovulation, thereby preventing pregnancy. Additional changes include increasing the thickness of the cervical mucus and providing an additional barrier, altering the endometrial lining that reduces the likelihood of implantation. The progestin component can vary in type and dose. In the phasic preparations, there may be 7 days of placebo pills that mimic a regular menstrual cycle. In the extended preparations, the cycle can be extended to once every 3 months to once a year. These preparations have advantages for women who have catamenial epilepsy. Common side effects include nausea, headache, breast tenderness, and breakthrough bleeding. However, venous thromboembolism (VTE) represents the most serious side effect and this risk increases in the setting of advancing age, smoking, and prior history of VTE. Historically, the dose of EE has been reduced to minimize these side effects.

Alternatively, there are progestin-only preparations for those for whom EE is contraindicated or not tolerated. Progestins have a variety of delivery systems including oral, intramuscular injections once every 3 months, and a device implanted subcutaneously. Maintaining levels of progestin mimics the pregnant state and prevents pregnancy. Side effects of progestin agents include irregular menstrual bleeding, weight gain, and changes in mood. Other devices such as patches, vaginal rings, and intrauterine devices (IUD) are also available for those who have difficulty or do not want to take a daily medication. The amount of hormone in the vaginal ring and IUD is lower and meant to be released locally, but there have been measurable levels systemically.

### Medications and Hormonal Contraception

Of greater concern to WWE is the interaction of AEDs on combined oral contraception (COC) when it is used to prevent pregnancy. In the general population, estimated failure rates are 0.3% under ideal conditions and up to 8% with real-world experience (8). The consequences of an unintended pregnancy in a woman with epilepsy on medications used to treat seizures are the increased risks of pregnancy and teratogenicity from the medications. Proper counseling should be given before starting any hormonal contraception. To compound the issue further, providers who treat WWE may not be familiar with the interactions between seizure medications and combined oral contraceptives and avoid the discussion or provide misinformation.

Lower hormone levels put women at risk of becoming pregnant. If a woman on a CYP450-inducing agent chooses a combined oral contraception (COC), then based on guidelines from the American Academy of Neurology (AAN) and American Epilepsy Society (AES), the ethinyl estradiol should be increased to 50 mg or the frequency of IM injections should be more frequent (Table 35.1). Currently the patches only have one dosage form and therefore are not recommended for this situation. Breakthrough bleeding mid-cycle may indicate low estradiol levels. When used exclusively for contraception, a second form of birth control such as barrier methods (eg, condoms (male and female), diaphragm, and cervical caps) and sterilization may be necessary to prevent pregnancy. Most women prefer this method exclusively due to the increased availability, no prescription, and no interactions despite the increased failure rate. Medications that inhibit hepatic

enzymes do not have any documented effect on COC effectiveness so doses of medications do not need to be adjusted.

### Hormonal Contraception on Medications

Most hormones have no effect on medications used to treat seizures. Lamotrigine levels can be reduced by about 50% by either natural or synthetic estrogens. Estrogen increases the metabolism of glucuronidation by uridine-diphosphate glucuronosyltransferase (UGT1A4) of lamotrigine before renal elimination. If a woman doing well on lamotrigine considers taking COC, then a baseline drug level would represent the target level for dose adjustment, which could be as much as a doubling of the dose. Follow-up drug levels about a week later should be done to ensure that the target level was achieved. Some women can have toxic side effects during the placebo week when there no estradiol is present. However, the higher levels can be advantageous in those women who have more seizures around their menstrual cycle. The devices impregnated with hormones release locally but there have been low measurable systemic levels and for those sensitive to these medications there may be a slight dose adjustment if they have more seizures. Progestin-only compounds do not alter lamotrigine levels, but there have been some studies to suggest that lamotrigine slightly lowers the area under the curve for progesterone by about 12%. It is not clear what the clinical implications by this slight reduction.

### Hormonal Contraception on Seizures

Despite theoretical concerns that estrogens have proconvulsive properties based on animal data, there have not been any studies to suggest that COC increase the risk of seizures. Some providers may start with a progesterone-only agent for their potential anticonvulsive properties.

Given the number of forms and combinations of contraception currently available, further study is needed to determine the relationship between COC and seizures so we have more data available to be able to advise WWE about their hormonal choices. WWE who have tried various birth control methods can enroll in the Epilepsy Birth Control Registry on line that has been established to gather data regarding safety and efficacy, the decision-making process, and best practices. Most WWE take medications to control their seizures, but not all providers who care for these women are aware of the interactions between seizure medications and hormones. Providers and women tend to avoid the conversation. If some seizure medications make the contraception less effective, then the consequence of an unintended pregnancy is compounded by the additional teratogenic effects of some of the medications used for the treatment of seizures.

**TABLE 35.1 Oral Contraceptive Preparations With High-Dose Estrogen**

	PROGESTOGEN (MG)	ESTROGEN (MG)
Ogestrel	Norgestrel (0.5)	Ethinyl estradiol (0.05)
Quasense, jolessa	Levonorgestrol (0.15)	Ethinyl estradiol (0.05/0.01)

Source: Modified from Ref. (9). Reddy, DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. *Expert Review Clin Pharmacol*. 2010;3(2) 183–192.

### PREPREGNANCY COUNSELING

Ideally, counseling should begin as soon as a girl becomes of childbearing age, because over half of pregnancies are unplanned. Much of the discussion revolves around

anticipatory guidance regarding the planning of a pregnancy and prevention of various risks that can occur during pregnancy, labor, and delivery, and postpartum care.

Most women fear that their children will inherit their epilepsy. For most epilepsy syndromes, this risk is low because of the polygenic nature of inheritance and the variety of etiological and precipitating factors. For those who have specific genetic disorders, it would be reasonable to have a discussion with a genetic counselor.

### Folic Acid Supplementation

Folic acid supplementation has been recommended for all women of childbearing age at a dose of 400 mg to minimize the risk of neural tube defects. Many seizure medications also have antifolate properties. The amount recommended for WWE varies from 400 µg to 4–5 mg. In 2009 (10), the AAN and AES subcommittee reviewed the available evidence but there was not enough strength of data in the literature regarding the exact amount to recommend. Women who have a family history of neural tube defects should take higher doses. The higher doses of folate also tend to be suggested for women on valproic acid since the risk of neural

tube defects was higher with the use of this medication during pregnancy. Folic acid is water soluble and excessive amounts can be eliminated in the urine. After delivery, the dose should return to the lower 400 mg.

### Medications

Once a woman is ready to become pregnant, she should reevaluate the need for medication with her neurologist. The process of tapering medications should begin at least 1 year before conception, if possible. Those who had been seizure free for at least 9 to 12 months before conception tend to remain seizure free during pregnancy. If she needs to remain on medication to remain seizure free, then the goal should be monotherapy at the lowest dose to control generalized convulsions. The risk of major malformations increases in a dose-dependent manner with some medications and with polytherapy. She should also understand that the dose of medications might need to be adjusted over the course of the pregnancy to maintain therapeutic levels so she remains seizure free. In general, medication levels should be checked once a trimester and any time there are breakthrough seizures.

**TABLE 35.2 Table of Medications**

HEPATIC ENZYMES	PROTEIN BINDING*	CONTRACEPTIVE INTERACTION	PREVALENCE OF MALFORMATIONS**	PREGNANCY CORD/SERUM***	LACTATION BM/SERUM ***
Induce					
Carbamazepine	70%–80%	Yes	3.0%	0.78	0.36–0.6
Felbamate	22%–25%	Yes			
Oxcarbazepine	33%	higher doses	2.2%	0.92	0.5
Phenobarbital	20%–45%	Yes	5.5%	0.7–1	0.36–0.6
Phenytoin	90%–95%	Yes	2.9%	0.94–0.97	0.18–0.45
Primidone		Yes		0.88–0.99	0.7–0.9
Topiramate	13%–17%	Yes	4.2%	0.85–1.06	0.67–0.1.1
Inhibit					
Valproate	80%–90%	No	9.3%	1.71	0.01–0.1
Zonisamide	40%–60%	No	0		0.41–0.93
No change					
Gabapentin	<3%	No	0.7%	1.3–2.11	0.7–1.3
Lamotrigine	55%	reduces level	2.0%	0.6–1.3	0.55–0.77
Levetiracetam	<10%	No	2.4%	0.97–1.45	1.0–3.09
Pregabalin		No			
Tiagabine	95%	No			
Vigabatrin		No			

Abbreviations: BM/Serum, Breast milk to maternal serum ratio; Cord/Serum, Cord/maternal serum ratio

\*Bromfield EB, Cavazos JE, Sirven JI, ed. *Neuropharmacology of Antiepileptic Drugs*. In: *An Introduction to Epilepsy* [Online]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK2513/>. Accessed May 23, 2013

\*\*The North American Antiepileptic Pregnancy Registry Spring 2012 Newsletter. <http://www.aedpregnancyregistry.org/>. Accessed April 12, 2013.

\*\*\*Harden, CL, Pennell, PB, Koppel, BS, et al. Practice Parameter Update: Management issues for women with epilepsy: Focus on pregnancy (an evidence-based review): Vitamin K, folic acid and breast feeding. *Neurology*. 2009;73:142–149.



Despite prior discussions, the first reaction a woman has to confirmation of pregnancy is to stop taking her medications. This noncompliance results from the fear of harming the fetus with medications. By the time most women find out that they are pregnant, it is about 5 to 11 weeks gestation and the neural tube has been formed and major organogenesis has already occurred. Discontinuing medications would be ill advised for women still having active seizures because they are at risk for generalized seizures and status epilepticus. Generalized seizures and status epilepticus can cause harm to both the mother and fetus. An unplanned pregnancy is not automatically a medical indication for a therapeutic abortion. If a WWE understands the risks and wants to continue with the pregnancy, she should work with her doctors to optimize the outcomes for her and her unborn child.

### TERATOGENICITY

The issue of greatest concern for most women is the risk of harming her child as a result of her seizure medications. The risk of a major malformation in the general population has been estimated as 1.6% to 2.1% (11). The data compiled regarding teratogenicity of antiepileptic medications that have been accumulated have been based on retrospective studies and from a variety of registries from around the world and in collaboration with pharmaceutical companies. Estimates suggest the risk of malformations increases with monotherapy to 4.5% (OR 2.6) and with polytherapy to 8.6% (OR 5.1). Most of the malformations recorded are major congenital malformations that require medical or surgical intervention; however, some major malformations are not noted until after the registry has collected the data. The most frequently noted malformations are ventricular septal defects, cleft lip and/or palate, hypospadias, radial ray defects or phalangeal hypoplasia, and spina bifida. In contrast, a minor malformation is an abnormality that does not have significant medical consequences, but less data have been collected on these abnormalities. Only recently have there been studies evaluating the Neurodevelopmental Effects of AED (NEAD) in children of WWE to see if there are long-term consequences as a result of fetal exposure. The Health Outcomes in Pregnancy and Epilepsy (HOPE) forum has the goal to study these issues and other relevant issues.

### Registries

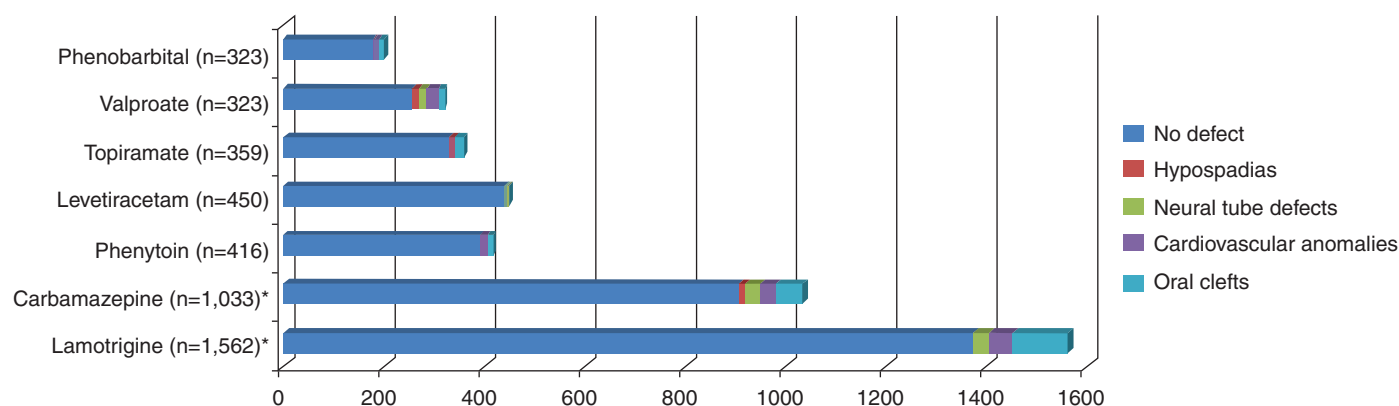
Each registry has different enrollment parameters and outcome measures. The two largest registries include the North American AED Pregnancy Registry and the European and International Registry of AED in Pregnancy (EURAP). The major difference in enrollment between the two registries: in the North American registry, the woman must call herself, while in the European registry, after a woman signs informed consent, the physician can enroll her and provide her pertinent medical information. Four countries also have birth registries. These registries continue to collect data and update continuously. An estimated 500 monotherapy

exposures are necessary to identify a major malformation. The advantage of several registries is consistent abnormalities in many registries represents a stronger signal. However, the disadvantage is that the data cannot be pooled because of the difference in the enrollment parameters.

### Malformation Estimates

Most of the retrospective data suggested that most of the older AEDs had increased risks of malformations and fetal AED syndrome associated with facial abnormalities. Since the registries have been established, accepted prospective data have greater significance over the potentially biased sampling of the older studies. Over several registries and reviews of current evidence in the literature (11), the most consistent finding is that valproic acid has higher risks estimated at 9.3% and specifically of cardiovascular abnormalities, spina bifida, hypospadias, and oral-facial abnormalities. Furthermore, these risks appear to be dose dependent and worse with polytherapy, specifically the combination of VPA and lamotrigine. Longer-term studies following children of women exposed to VPA show reduced cognitive outcomes, increased neurodevelopmental delays, and more frequent diagnosis of autism as a result of perinatal exposure. Phenobarbital has been associated with increased risks of cardiovascular abnormalities estimated at a rate of 2.5% compared to 0.19% in the baseline comparison group. In addition, phenobarbital is also associated with oral cleft and urogenital abnormalities. Phenytoin has been associated with cleft palate and digit hypoplasia. One study suggested that men of mothers with epilepsy who took phenobarbital had reduced cognitive abilities. Carbamazepine has been associated with increased risk of neural tube defects and posterior cleft palate; however, the prospective data suggest that the risks may be similar to the newer medications. The risk of diminished cognition of children of mothers with epilepsy was low if medications were not taken during pregnancy. The risk remains low despite the use of carbamazepine and possible with phenytoin.

Of the newer-generation medications, the data are still accumulating (12). Lamotrigine has been considered to be a fairly safe medication in pregnancy, but it, too, has an increased risk of oral clefts. The risk of oral-facial malformations for lamotrigine has been estimated at 2.0%. Conflicting data exist whether there may be a dose-related effect for lamotrigine. Early data for levetiracetam suggest an increase in the rate of malformation of 2.4%. Data on levetiracetam suggest that there are few malformations but even cumulatively the numbers of exposures are too small and none of the registries have yet to reach statistical significance. Topiramate also has an increased incidence of cleft lip but the frequency varies among registries and seems to be higher than the background population of unexposed pregnancies. There may also an increase in hypospadias with topiramate, though the outcomes appear reassuring. Similarly the numbers for the other AEDs are too small to have any definitive statements. Data from the North American registry trending



**FIGURE 35.2** North American AED pregnancy registry 1997–2011 data on prevalence of most common specific malformations among infants exposed to monotherapy AED diagnosed before the age of 5 days.

Source: Adapted from Ref. (12). Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012;78:1692–1699.

the use of AEDs during pregnancy demonstrates an increase in some of the newer medications (Figure 35.2). Continued enrollment in various registries should provide more data to establish an informed dialog with patients.

Future directions not addressed by the registries include the pathophysiology of the malformation and the reasons some fetuses are affected and others are not with similar exposures. Animal studies suggest that apoptosis may be a factor. Routinely medication doses require adjustment during the pregnancy and the impact of increasing dosages over the course of the pregnancy is not known. Prospective studies of developmental outcomes of children of mothers with epilepsy need to be done.

## PREGNANCY

There are over 1.5 million WWE in the United States and they give birth to 25,000 infants each year, representing 0.3% to 0.6% of all gestations, and over 90% of these infants have normal and healthy outcomes (13). Nonetheless, WWE have specific concerns about how their condition and the medications used to treat it will have an impact on their pregnancy and their developing fetus.

Currently, insufficient evidence exists regarding the change in seizure frequency or status epilepticus as a result of pregnancy itself. The majority of pregnant WWE, 50% to 83%, have no change in their seizure frequency during the pregnancy (13). Retrospective studies suggest 7% to 25% of women do better during pregnancy; and some women report that it is the only time they are completely seizure free. Theoretically, this may be related to the increased progesterone state of pregnancy that peaks at 36 to 38 weeks. However, 20% to 33% may experience an increase in seizures, which may be related to the physiological and physical changes

over the course of the pregnancy. There has been suggestion that seizures may increase in frequency during the last trimester.

## Pregnancy and Seizures

The consequences of a generalized seizure during pregnancy include the risk of a fall causing rupture of membranes and maternal hypoxia with acidosis, which can be transmitted to the fetus. These changes can increase the morbidity and mortality for both the mother and fetus, and result in a spontaneous abortion (less than 20 weeks) or stillbirth (fetal loss greater than 20 weeks). A United Kingdom study that reviewed causes of maternal death suggested that the increased mortality may have been associated with WWE who stopped taking their medications. However, prospective data from EURAP has not shown any significant consequences to a generalized convulsion so far. Nonconvulsive seizures have been reported to increase fetal heart rate, but there have been no reports of significant injury or harm unless the seizure resulted in an accident. The incidence of status epilepticus in the EURAP registry is about 2% with convulsive status representing a third of the cases (13). There was one stillbirth and no maternal deaths noted.

## Pregnancy and Medications

The physiological changes during pregnancy impact the pharmacokinetics of medication management. Reduced intestinal absorption, increased plasma volumes, decreased protein binding, altered metabolism, and increased drug clearance result in changes in drug levels over the course of pregnancy, typically putting a woman at risk for seizures. Medications with the most evidence for close laboratory

follow-up include lamotrigine, carbamazepine, and phenytoin. Enhanced glucuronidation during pregnancy increases lamotrigine clearance, especially during the second trimester. Although the percent and rate of change varies on an individual basis, on average, there is over a 30% reduction and most women are symptomatic with over a 65% drop (14). Current recommendations suggest checking at least baseline levels of AEDs before pregnancy, while the WWE is under optimal control. This level should represent the target level over the course of pregnancy. Since the levels can change in an unpredictable manner, they should then be checked more frequently than any other medications to maintain that target level. At times, monthly or more often, levels may be necessary especially if frequent adjustments need to be made or with breakthrough seizures. Postpartum, the clearance recovers within days of delivery and doses should be readjusted back to prepregnancy doses or the new mother will feel the toxic effects of dizziness and diplopia.

Carbamazepine levels reduce by 9% during the second trimester and up to 12% by the third trimester due to enhanced clearance. Phenytoin total levels fall over the course of the pregnancy related to increased clearance, but the free fraction of the medication can increase over the second and third trimesters due to reduced protein binding. Following both free and total levels are recommended to make dose adjustments accordingly. Less data are available for oxcarbazepine, but it is also metabolized through glucuronidation pathway. The 10-monohydroxy derivative (MHD) levels have been shown to drop by 61.5% during the second trimester. The levels should be checked and appropriate dose adjustments should be made. There are data to suggest the levetiracetam levels fall during pregnancy but the implications are not as clear. Insufficient data exist for phenobarbital, VPA, primidone, and ethosuximide.

All of the medications used to treat seizures cross the placenta and therefore the fetus will be exposed. The rate at which medications are transferred across the placenta is measured by the neonatal/maternal concentration, and a transfer rate of 0.6 is considered clinically relevant. Medications measured at this rate include phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, and VPA. In the current literature, data may possibly suggest clinically relevant transfer for gabapentin, lamotrigine, oxcarbazepine, and topiramate. There was not enough information regarding the placental transfer of ethosuximide.

### Obstetric Issues

Women with epilepsy have increased complications and risk during pregnancy over the general population (15). Hyperemesis gravidarum can prohibit some women from maintaining steady serum levels of medications, especially if severe. Most women can keep their medications down if they have small meals with their medications. However, if they require admission to maintain hydration, some of the seizure medications have intravenous formulations and can be supplemented.

Anatomic monitoring with fetal ultrasound has been recommended between 12 and 22 weeks. In conjunction with an alpha-fetoprotein level, an early study can identify neural tube defects between 15 and 16 weeks. These studies can be followed by late anatomic ultrasound for cardiac and limb abnormalities. Identification of major malformations allows for appropriate planning at the time of delivery and alerting the appropriate neonatal team to participate in the birth plan.

In the past, concerns were raised about increased rates of intracranial hemorrhage within 24 hours of birth to neonates exposed to enzyme-inducing medications. These hepatic enzymes increase the metabolism of vitamin K-dependent clotting factors. Vitamin K supplementation was recommended starting around 36 to 38 weeks at a dose of 10 mg a day. However, on critical analysis of the medical evidence, there was insufficient evidence to support or refute this practice for infants older than 34 weeks. Furthermore, it is standard practice for all neonates routinely to receive vitamin K (1 mg) intramuscularly at the time of delivery.

### Delivery Concerns

Previous concerns suggested that WWE had a higher risk of premature contractions and labor (16). The available evidence does not suggest that this is still the case. Their babies were twice as likely to be small for gestational age especially if the woman smoked during pregnancy. There has been retrospective data suggesting that the risk of placental abruption may be higher. Preeclampsia has been shown to be more likely. WWE fear having a seizure during delivery. This fear can be fueled by the anticipated pain, changes in respiration, and fatigue of active labor. The risk of eclampsia is not clear, because a typical seizure in this setting can be misdiagnosed as eclampsia. There has been a demonstrated increased risk of having a cesarean section. If a seizure occurs during labor, then the woman should be stabilized prior to consideration of emergency cesarean section. There is also a higher risk of an Apgar score of less than 7 at 1 minute. The risk of perinatal death is not increased.

### POSTPARTUM CONCERNS

Once the baby is born and returns home with the mother with epilepsy, new challenges face her in terms of her own care and the childcare. Modifications in her medications especially if they were increased during the pregnancy will need to be performed and levels checked. Feeding choices will impact the care and the well-being of the mother with epilepsy. Participating in the daily care activities may need to be modified for both the mother and father with epilepsy.

### Lactation

Current recommendations suggest 12 months of breast feeding to provide maternal bonding, conferred immunity for infectious diseases, and prevention of immune-related

disorders, reduced infant mortality, and influence of cognitive development (14). Decisions regarding feeding the infant revolve around continued exposure to medications and sway many women and providers from recommending breastfeeding despite the benefits. Although the infant was already exposed to the medications in utero, the mother was responsible for the clearance of the medications. Postpartum, the infant would metabolize and excrete the medication on its own. There may be toxic metabolites that the mother would have already eliminated. The effects of AEDs through breast milk are not known in the neonate.

Lactation involves active transport of nutrients into the breast milk. Medications that are highly protein bound have lower concentrations in the breast milk compared to medications that are less protein bound. Medications that are of low molecular weight and more lipophilic with high oral bioavailability are more likely to have higher concentrations in breast milk. In general, the older drugs were highly protein bound and thus had lower levels in breast milk compared to maternal concentrations. The newer medications have a breast milk /maternal serum concentration ratio closer to 1.0. Despite this, the infant serum concentrations have been measured to be lower than the maternal serum concentration. If the infant is too sedated to suck and feed, then that should represent a clinical sign that breastfeeding should not be continued for the infant's sake.

### Child Care

Frequent nighttime feeds can lead to sleep deprivation in the parent with epilepsy, which might trigger more seizures. Having a partner or a family member to assist with some of these feedings can improve overall quality of life and still allow the new parent to participate in their infant's care without the added concern of more seizures. Taking naps with the infant can also prevent the fatigue associated with the care of an infant.

If the parent with epilepsy is still having seizures, changes in the routine care of the infant can still allow them to participate without the risk of injury to parent or infant. If the parent loses awareness during their seizures, then they should not carry the baby in their arms but rather transport the infant in a small stroller that can be wheeled within the house. Diaper changes can be done on a mat on the floor rather than a changing table to reduce the risk of falls. Feedings can be done with supportive devices. A parent with epilepsy should not bathe the infant alone but should wait for supervision because of the risk of drowning in just a few inches of water. Alternatively, they could give the infant a sponge bath instead. No one should attempt to cook while holding an infant. When the baby becomes mobile, ensure that safety gates are available to keep them from falling down stairs, and secure doors so they cannot get out inadvertently if the parent loses awareness for a few minutes.

Most PWE want the full experience of life including the ability to have children. At times, they must traverse many challenges to achieve this goal. Having a knowledgeable provider to assist them anticipate and overcome some of these issues can ease their anxiety.

The first challenge PWE face is to develop a relationship. Encouraging PWE to participate in community activities can minimize depression and facilitate social interactions, thereby reducing the isolation they experience. By being open and nonjudgmental when PWE express concerns about sexuality and fertility, a neurologist can encourage PWE to consider changes in medications, pursue endocrine, urological or gynecological evaluations, and get appropriate treatment. Many PWE feel the choice of contraception is an important issue but feel shuttled between their neurologist, gynecologist, or primary care provider about the decision. Understanding the interactions between medications and hormones can alleviate this barrier and open communication. If the woman does not initiate the discussion, then about half will not have a discussion at all and could be at risk for unplanned pregnancies. More couples are open and want to facilitate a dialog before pregnancy. The information reviewed includes supplementation with folate, medication use, and risks of malformations. The provider needs to understand the type of epilepsy syndrome, the optimal medication for that syndrome at the lowest doses, and appropriate monitoring levels during the course of the pregnancy. Pregnancy under the best of circumstances is fraught with anxiety. Providing advice about the changes specifically in a PWE that can occur during pregnancy, delivery, and after the baby is born alleviates many fears. This advice also allows the family to provide adequate care to support the newborn and the new parent with epilepsy.

Supporting PWE requires a team of providers. As a neurologist, both patients and other providers rely on specific information regarding the epilepsy syndrome, the medications used to treat it, and interactions with other medications to make decisions regarding reproductive issues in PWE. Having the most updated information allows the neurologist to participate in providing the most accurate and appropriate care for the person with epilepsy.

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# Bone Health

*Christa B. Swisher and Aatif M. Husain*

It was first reported about 40 years ago that antiepileptic drugs (AEDs) were associated with poor bone health, such as osteoporosis and pathologic fractures. Previously, osteoporosis was thought to be primarily a disease of older women; however, studies have found that men with epilepsy treated with AEDs are also susceptible to the development of bone disorders (1). In addition, it has been shown that children with epilepsy taking AEDs can also develop bone disease (2). As the population ages, bone health will become an increasingly important issue for patients with epilepsy.

The issues pertaining to bone health in epilepsy patients are unfortunately still underrecognized. Despite the growing body of literature linking chronic AED therapy and poor bone health, a survey showed that only 28% of adult and 41% of pediatric neurologists perform screening for bone disease in their epilepsy patients (3). Further research must be performed to determine the optimal method and timing of screening and to identify the most effective treatment. This chapter will discuss the pathophysiology of bone metabolism, an overview of osteoporosis, the relationship between epilepsy and bone loss, the effect of various AEDs on bone health, and the current methods for screening and treatment of bone health in patients with epilepsy.

## **PATHOPHYSIOLOGY**

### **Bone Structure and Metabolism**

Bone is a dense connective tissue and has three main categories of function: mechanical, synthetic, and metabolic. Although the mechanical and synthetic properties are important to providing structural support and the production of blood components, this chapter will primarily focus on the metabolic properties of bone. The metabolic function of bone primarily includes the storage of minerals (most notably calcium and phosphorous), fat, and growth factors. In addition, bones function as an endocrine organ involved in the control of phosphate metabolism.

The formation and breakdown of bones is a constant, dynamic process referred to as bone turnover or remodeling. Interestingly, approximately 10% of the skeletal mass of

an adult is remodeled each year (4). Osteoblasts and osteoclasts are the cell types that function to remodel bone with the goal of maintaining calcium homeostasis and repair of micro-damages in bone. Osteoblast activity results in bone formation and osteoclast activity results in resorption of the bone matrix. These two processes occur simultaneously and are closely linked. Osteoclasts remove bone by acidification and proteolytic digestion. After this occurs, osteoblasts then initiate bone formation by secreting osteoid, which eventually becomes mineralized into new bone. Growth factors, cytokines, systemic hormones, and mechanical signals determine the development and differentiation of osteoblasts and osteoclasts (4). The balance of osteoblast and osteoclast activity determines bone mineral density and how well bone homeostasis is maintained.

### **Calcium Metabolism**

There is normally 1 to 2 kg of calcium present in the adult body and over 99% of this resides in the skeleton. Skeletal calcium provides stability to bones and also functions as a reservoir of calcium needed elsewhere in the body. Skeletal calcium reaches its peak values in early adulthood and then gradually declines by 1% to 2% per year (5).

About 0.5% to 1% of total body calcium is readily available in the extracellular fluid as ionized calcium. The calcium concentration in blood is normally 2.2 to 2.6 mM (8.5–10.5 mg/dL) and about 50% of this is in the form of ionized calcium. In the extracellular fluid, the concentration of ionized calcium must be kept within a narrow range (1.1–1.3 mmol/L). The rest of calcium is bound to negatively charged proteins (primarily albumin and immunoglobulins) or complexed with phosphate, citrate, sulfate, or other anions (5). Since calcium is heavily protein bound, blood calcium concentration can be affected by changes in protein level and acidosis.

The level of ionized calcium concentration is affected by parathyroid hormone (PTH) and vitamin D in the form of 1,25-hydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ) by modifying the rate of calcium movement across intestinal and renal epithelia (5). In turn, ionized calcium in the blood also affects levels of PTH and  $1,25(\text{OH})_2\text{D}$ .

The intake of dietary calcium in a typical American diet can range widely from 10 to 37 mmol/d (400–1,500 mg/d) (5). Calcium is absorbed from the GI tract via active and passive mechanisms. The active mechanism accounts for 95% of dietary calcium absorption and is primarily controlled by  $1,25(\text{OH})_2\text{D}$ . The presence of gastric acids is necessary for calcium absorption.

### Phosphorous Metabolism

The average amount of total body phosphorous is 600 g and the majority of this is contained in bone mineral. The rest is contained in the intracellular compartment as free anions and as a component of organophosphate compounds, which include proteins, nucleic acids, adenosine triphosphate (ATP), and carbohydrates. In serum, approximately 12% of phosphate is bound to protein. The normal blood concentration of phosphate is 0.75 to 1.45 mmol/L (2.5–4.5 mg/dL).

Phosphate is present in many foods and absorbed easily from the GI tract, even in the absence of vitamin D. However, the absorption of phosphate is increased by  $1,25(\text{OH})_2\text{D}$ . Low levels of circulating phosphate stimulates the renal production of  $1,25(\text{OH})_2\text{D}$ . Phosphate levels are primarily regulated by the renal resorption or excretion of filtered phosphate.

### Hormones: Vitamin D and Parathyroid Hormone

The two main hormones that control calcium homeostasis are vitamin D and PTH. Vitamin D and its metabolites are actually hormones since they can be synthesized endogenously. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D (25OHD), which is then metabolized in the kidney to  $1,25(\text{OH})_2\text{D}$ , the biologically active form. Vitamin D increases dietary calcium absorption and bone mineralization.

PTH has actions on bone, kidney, and intestinal mucosa. PTH increases bone remodeling by stimulating osteoclast activity and thus resulting in loss of calcium from bone. PTH increases calcium resorption in the kidneys and also increases GI absorption of calcium.

Calcitonin is another hormone involved in calcium homeostasis. Numerous other hormones are involved in calcium homeostasis, such as estrogen, androgen, glucocorticoids, and thyroid hormone (4).

## OSTEOPOROSIS

Osteoporosis is characterized by low bone mass and an increased risk for fractures. The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviations or more below the mean peak bone mass of young, healthy adults as measured by dual-energy X-ray absorptiometry (DEXA). This reduction in BMD may or may not be associated with the presence of fragility fractures. Osteoporosis is classified as primary (type 1 or type 2) or secondary. Primary type 1 is postmenopausal

osteoporosis. Primary type 2 is also known as senile osteoporosis and occurs in both males and females after the age of 75. This type is more common in females than in males (2:1).

Secondary osteoporosis can occur at any age and affects women and men at similar rates. There are numerous causes of secondary osteoporosis. Some common causes include renal insufficiency, immobilization, various endocrine disorders, malnutrition, and the use of certain medications such as glucocorticoids, antidepressants, and AEDs. A list of common secondary causes of osteoporosis is shown in Table 36.1.

**TABLE 36.1 Secondary Causes of Osteoporosis**

- Endocrine disorders
  - Hypogonadism
  - Hypercortisolism
  - Diabetes mellitus
  - Growth hormone deficiency
  - Estrogen deficiency
  - Hyperthyroidism
  - Hyperparathyroidism
  - Hyperprolactinemia
  - Low testosterone
  - Calcium deficiency
  - Adrenal insufficiency
- Renal disorders
  - Chronic renal insufficiency
- Gastrointestinal disorders
  - Inflammatory bowel disease
  - Celiac disease
  - Cirrhosis
  - Chronic liver disease
- Hematologic disorders
  - Multiple myeloma
  - Lymphoma
  - Leukemia
- Nutrition
  - Vitamin D deficiency
  - Alcohol
  - Malabsorption syndrome
  - Anorexia nervosa
- Medications
  - Glucocorticoids
  - Antidepressants
  - Heparin
  - Anticonvulsant drugs
  - Cyclosporine
  - Chemotherapy
  - Diuretics
  - Lithium
- Genetic syndromes
  - Osteogenesis imperfecta
  - Marfan syndrome
  - Ehlers-Danlos syndrome
  - Homocystinuria
  - Glycogen storage diseases
- Other
  - Cigarette smoking
  - Cystic fibrosis
  - Physical inactivity
  - Pregnancy

Osteopenia is defined by the WHO as bone density one standard deviation or more below that of average of young, healthy adults. The use of this term is controversial since many patients with osteopenia will not go on to develop osteoporosis. The International Society for Clinical Densitometry (ISCD) recommends avoiding the use of the term osteopenia. These patients are now referred to as having low bone mineral density (BMD).

## EPILEPSY AND OSTEOPOROSIS

### Overview

There have been several retrospective, case-control, and cross-sectional studies that have shown higher rates of osteoporosis and low BMD in adult and pediatric patients with epilepsy when compared to age-matched nonepileptic controls (6). The approximate rate of low BMD or osteoporosis in patients with epilepsy treated with AEDs is 38% to 60% (7–9). In a 2005 meta-analysis, there was a significantly lower BMD in both the spine and hip in patients with epilepsy taking AEDs when compared with age-matched controls (10).

Aside from a direct effect of AEDs on bone health, patients with epilepsy may have additional risk factors for the development of osteoporosis. Immobility and inactivity are strong risk factors for osteoporosis. Participation in weight-bearing exercise has been shown to improve BMD. Many patients with epilepsy are immobile or inactive and not able to participate in weight-bearing exercise, placing them at an increased risk for osteoporosis. The lack of weight-bearing exercise may be due to various physical and cognitive deficits. In addition, patients with epilepsy and physical restrictions may have limited exposure to sunlight, which is the primary source for vitamin D. Furthermore, patients taking carbamazepine may develop a sunlight-induced rash and limit their sunlight exposure to prevent such a rash.

### Fractures

Patients with epilepsy often experience bone fractures in the setting of seizures, either from seizure-related falls or trauma due to altered mental status (ie, motor vehicle collision). Studies have shown that patients with epilepsy are 2 to 6 times more likely to experience a fracture than the general population in the United States (11). This fracture risk is similar to the fracture risk seen in patients taking chronic steroids. In a meta-analysis, there was a higher fracture risk in patients with epilepsy compared to the general population (relative risk of any fracture 2.2, 95% CI 1.9–2.5) (10). There was an increased relative risk for all fractures studied: hip, forearm, and spine. However, the overall increase in fracture risk was higher than expected from the BMD values. The authors postulated that seizures might account for the higher than expected fracture risk since one-third of all fractures were associated directly with seizures. However, about two-thirds of falls in patients with epilepsy are not

related directly to seizures. Why patients with epilepsy have a higher rate of falls when compared to age-matched controls is unknown. It has been postulated that epilepsy may be associated with other neurologic deficits such as weakness, impaired sensation, poor balance, and impaired cognition, leading to an increased susceptibility to falls. AEDs often have side effects such as ataxia and drowsiness, which may contribute to epilepsy patients having an increased risk of falls and fractures.

There is a higher rate of fractures in patients with epilepsy who receive prescriptions for rectal benzodiazepines, have AED polypharmacy, and have more medical visits (1). These factors are all associated with a greater severity of epilepsy. In addition, there is a higher fracture risk in older patients with epilepsy. Among epilepsy patients, it is not clear if there is a higher risk of fractures in men or women since the data are variable (1).

### Antiepileptic Drugs

The use of antiepileptic drugs has been shown to be an independent risk factor for the development of low BMD (6,10). Although there is a consensus that patients with epilepsy taking AEDs have higher rates of bone loss and pathologic fractures, the exact mechanism has not been identified. The data on calcium concentrations has been inconsistent, with some studies reporting reduced calcium concentrations and other studies showing no significant effect on calcium levels. Overall, most studies have shown normal calcium concentrations in this patient population (12). Although studies have not been able to show a consistent effect on vitamin D concentration, the majority of studies shown that vitamin D levels are reduced in patients taking AEDs, particularly in patients taking enzyme-inducing AEDs (12). PTH elevation may cause low BMD in patients taking AEDs by increasing bone resorption, but, again, studies have had inconsistent results regarding the levels of PTH in a patient taking AEDs (6). It has been theorized that AED-treated patients are resistant to PTH action on bone, due to several observations that PTH levels are increased in the presence of decreased or normal serum calcium concentration (12).

Table 36.2 lists the potential mechanisms for AED-induced bone loss. Despite the inconsistent results regarding the mechanism of bone loss in patients with epilepsy, there have been consistent results showing elevations in bone resorption markers associated with the use of AEDs. This suggests that there is long-term increased bone turnover that eventually leads to loss of BMD. In addition to increased bone turnover, studies have shown that phenytoin and carbamazepine inhibit cell growth in bone cell cultures taken from surgical patients (13). Studies in children with epilepsy taking AEDs have demonstrated poor bone formation (2). These data suggest that both increased turnover and impaired synthesis are mechanisms by which AED use leads to decreased BMD.

There does appear to be a sex difference regarding the effect of AEDs on BMD with women showing a more marked decline in BMD when compared with men (3). In



**TABLE 36.2 Possible Mechanisms of AED-Induced Bone Loss**

- Altered vitamin D metabolism
  - Accelerated vitamin D metabolism
  - Inactivation of vitamin D
- Altered calcium metabolism
  - Reduced intestinal absorption
- Alteration in PTH metabolism
  - Elevation in PTH levels
  - Inhibition of cellular responses to PTH
- Direct action of AEDs on osteoblasts
- Altered sex steroid metabolism
- Reduction in calcitonin levels
- Vitamin K deficiency
- Direct stimulation of osteoclast activity
- Alteration in leptin signaling

addition to the type of AED a patient is taking, AED polypharmacy appears to be an independent risk factor for the development of fractures (2). In a meta-analysis, the duration of AED use was also shown to be associated with an increased risk of fractures, particularly in women (10).

#### *Enzyme-Inducing AEDs Versus Non-Enzyme-Inducing AEDs*

P450 enzyme-inducing AEDs are most commonly implicated in reducing BMD. Phenytoin, carbamazepine and phenobarbital appear to be associated with reduced BMD, possibly due to their effect on hepatic enzyme induction. There is accelerated metabolism of vitamin D and secondary hyperparathyroidism when the hepatic P450 enzyme system is activated (2). Studies have shown that enzyme-inducing AEDs affect vitamin D metabolism and may predispose patients to bone loss (12). This effect on vitamin D metabolism may lead to hypocalcemia and hypophosphatemia. AEDs may also inhibit the cellular response to PTH. All enzyme-inducing AEDs do not have the same effect on BMD, suggesting that further research is needed to look beyond the mechanism of enzyme induction. In addition, enzyme-inducing AEDs negatively affect reproductive sex steroids, which may secondarily result in loss of BMD.

Non-enzyme-inducing AEDs have also been inconsistently associated with a reduction in BMD. The mechanism by which non-enzyme-inducing AEDs result in bone loss has not been identified, but studies have suggested they alter osteoblastic function (2). When used in children, valproate (VPA), a hepatic enzyme inhibitor, has been associated with a 10% or greater reduction in BMD when compared with age-matched controls (2). Of the non-enzyme-inducing AEDs, the majority of the studies have focused on the effects of VPA. Studies suggest that VPA reduces BMD possibly by stimulating osteoclast activity.

Although there appears to be a higher rate of osteoporosis in patients taking enzyme-inducing AEDs when compared to patients taking non-enzyme-inducing AEDs, case-control

studies have not shown a difference in the fracture risk when the use of enzyme-inducing AEDs was compared to the use on non-enzyme-inducing AEDs in patients with epilepsy (12).

#### *Carbamazepine*

A majority of the evidence shows that chronic use of carbamazepine leads to a reduction in BMD. Carbamazepine has been associated with decreased levels of 25OHD, elevated PTH, and increased bone turnover. Owing to these observations, patients with long-term carbamazepine use should have regular screening of vitamin D levels. In addition, administration of calcium and vitamin D supplementation should be considered (14).

#### *Phenytoin*

Phenytoin has been associated with reduction in BMD and an increased risk of fracture. This effect may increase with longer duration of therapy. Typical lab abnormalities of adult and pediatric patients taking phenytoin include hypocalcemia, hypophosphatemia, low vitamin D levels, elevated PTH, and increased markers of bone turnover. The adverse effect of phenytoin on BMD appears to be higher in postmenopausal women and in older males. Given these findings, patients on chronic phenytoin therapy should have regular screening labs for bone loss and monitoring of BMD by DEXA. In addition, providers should consider early, prophylactic therapy with vitamin D supplementation (14).

#### *Phenobarbital*

Studies have demonstrated that long-term use of phenobarbital is associated with the loss of BMD and an elevated risk of fracture. The mechanism by which this occurs may be due to a downregulation of 25-hydroxylation. Phenobarbital does not appear to affect serum levels of calcium and phosphorus. Routine screening with DEXA and administration of prophylactic vitamin D is warranted in patients taking phenobarbital (14).

#### *Valproic Acid*

Although some studies have found that VPA had no effect on BMD values, the majority did show that BMD was adversely affected by VPA. The response appears to be dose-dependent. The effects of VPA on calcium and phosphate levels are controversial. Some studies have shown that serum 25OHD concentrations are reduced in patients taking VPA, but the effects of VPA on BMD cannot be fully explained by vitamin D metabolism since VPA is not an inducer of the hepatic P450 enzyme system. VPA appears to have less of a negative effect on BMD as compared to carbamazepine and phenytoin. Patients on VPA therapy should have BMD monitoring with DEXA (14).

#### *Lamotrigine*

Longitudinal studies evaluating the effects of lamotrigine monotherapy showed that there is no effect on BMD. There

does not appear to be any alteration in the levels of calcium, 25OHD, or markers of bone turnover in patients taking lamotrigine (14).

### *Gabapentin*

No studies have evaluated the effects of gabapentin monotherapy on bone metabolism. However, in studies prospectively evaluating patients taking several AEDs, it has been suggested that gabapentin is associated with an increased risk of low BMD. Abnormalities in laboratory makers of bone metabolism have not been identified in patients taking gabapentin (14). It is not clear from the literature if these patients should have regular BMD screening.

### *Levetiracetam*

Further studies are necessary to fully understand the effect of levetiracetam on bone health. One study of a small number of patients taking levetiracetam monotherapy showed no effect on vitamin D levels or BMD. However, animal studies have shown reduced bone strength and reduced bone formation without an effect on BMD (14).

### *Oxcarbazepine*

Similar to carbamazepine, oxcarbazepine has been shown to reduce BMD. Laboratory test abnormalities associated with oxcarbazepine use are reduced levels of 25OHD and elevated markers of bone turnover. Regular screening of bone health is warranted in patients on long-term oxcarbazepine therapy (14).

### *Topiramate*

There are little data reporting the effect of topiramate on BMD. One cross-sectional study demonstrated that topiramate monotherapy was associated with increased bone turnover, hypocalcemia, and reduced PTH without an effect on BMD or vitamin D metabolism in premenopausal women with epilepsy (15). A double-blind, randomized trial of topiramate as treatment for obesity showed no changes in markers of bone turnover (6). Although more data are needed, routine screening of bone health may be warranted in patients prescribed chronic topiramate therapy.

### *Zonisamide*

Data evaluating the effects of zonisamide on bone health in patients with epilepsy are lacking, but animal studies have shown that zonisamide administration is associated with a reduction in BMD possibly secondary to accelerated bone resorption.

## **Special Patient Populations: Women**

Women with epilepsy are at a particularly high risk for the development of osteoporosis after menopause due to estrogen deficiency when compared with men. The presence

of AEDs may predispose them to an even higher risk of osteoporosis and insufficiency fractures when compared to nonepileptic women. Given that more than 50% of Americans over the age of 50 will be at risk for a fracture, postmenopausal women with epilepsy are at an alarmingly high risk.

## **Special Patient Populations: Pediatrics**

Given that BMD gradually increases over time and reaches a maximum at young adulthood, childhood and adolescence are critical periods for bone formation and mineralization. If peak BMD is not achieved, there is a greater risk in the future for fractures and the development of osteoporosis. Low BMD is present in most nonambulatory children with cerebral palsy by 10 years of age (2). Fractures occurred in approximately 25% of children older than 10 years who were severely affected. Several factors have been associated with the development of low BMD, in decreasing order of importance: severity of impairment, difficulty with feeding, used of AEDs, and lower triceps skinfold z scores.

In addition to epilepsy, many pediatric patients also have other medical issues that can adversely affect bone health. These include renal impairment, skeletal hypoplasia, and reduced physical activity. Another factor that is likely associated with the occurrence of fractures is poor coordination and ataxia from AED side effects and/or from a coexisting neurologic condition.

## **SCREENING**

Currently, no guidelines exist regarding which patient populations with epilepsy should be screened for bone loss. Given that numerous AEDs have been implicated in causing BMD loss, it is reasonable to counsel all patients taking AEDs about bone health. This is particularly important in epilepsy patients who have other risk factors for bone loss, such as patients who are immobile or women who are postmenopausal.

BMD is typically assessed using a DEXA scan. Quantitative ultrasound (QUS) is another way BMD can be assessed. The available screening labs for evaluation of bone health are serum concentrations of calcium, ionized calcium, phosphorus, 25OH vitamin D, 1,25(OH)<sub>2</sub>D, and 25(OH)D<sub>3</sub>. Other markers include alkaline phosphatase, serum osteocalcin, and urinary N-terminal telopeptide, which assess bone matrix turnover. Laboratory evaluation of reproductive sex hormones includes follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, estradiol, and sex hormone binding globulin.

In the general population, it is unclear what role the previously listed biochemical tests should have in the diagnosis and monitoring of osteoporosis. There are no consensus guidelines regarding which laboratory tests should be obtained for bone loss screening in patients with epilepsy taking AEDs. Given that patients with epilepsy taking AEDs have a higher risk for bone loss than the general population, it has been recommended that laboratory screening should

occur at baseline with monitoring of serum calcium, phosphate, alkaline phosphatase, PTH, and 25OHD (3).

Although tests are available for vitamin D and its metabolites, typically only 25OHD is obtained to assess for the risk of bone loss. The optimal serum 25OHD concentration is controversial. Some experts recommend maintaining serum 25OHD concentration between 20 and 40 ng/ml (50–100 nmol/L), but others suggest 25OHD levels between 30 and 50 ng/ml (75–125 nmol/L) (16).

### Dual-Energy X-Ray Absorptiometry

DEXA remains the gold standard for the diagnosis of osteoporosis in any patient population. It is a way of measuring BMD that utilizes two X-ray beams with different energy levels aimed at the patient's bone. This technique uses radiation, but the radiation dose is about 1/10 that of a standard chest X-ray. DEXA scanning is typically performed at the hip, spine, and forearm and takes approximately 10 to 20 minutes. DEXA measures bone mineral content (BMC, in grams) and bone area (BA, in cm<sup>2</sup>). The BMD is calculated by dividing the BMC by BA. The DEXA scores are reported as T-scores and Z-scores, which are the number of standard deviations from the mean peak BMD for a given population. The T-score is a comparison of a patient's BMD with that of a healthy 30-year-old of the same sex. The Z-score is a comparison of a patient's BMD with that of an average person of the same age and sex. As stated previously, a T-score of -2.5 or lower is consistent with osteoporosis. A T-score of -1.0 to -2.5 is consistent with low BMD (previously referred to as osteopenia). The fracture risk correlates well with the T-score and increases twofold with each standard deviation decrease in BMD.

It has been suggested that a DEXA scan be obtained in all high-risk adult patients with epilepsy before initiation of AED treatment (3). These include postmenopausal women and patients with multiple risk factors for osteoporosis.

### Quantitative Ultrasound

There are several advantages of QUS over DEXA that includes lack of radiation, cost, ease of use, and portability. It has been suggested that, unlike DEXA, QUS can independently predict fracture risk (17). QUS is able to assess information about bone density by measuring the change in velocity and amplitude of the sound waves when they travel through bone tissue. QUS typically measures bone density at the heel.

Studies have been performed with QUS showing that it is a feasible way to evaluate bone density (17). There have been numerous studies evaluating the sensitivity and specificity of QUS in comparison with DEXA for the diagnosis of osteoporosis in all patient populations, and the results have been mixed. A meta-analysis of 25 studies concluded that the sensitivity and specificity of QUS was too low to diagnose osteoporosis as determined by DEXA (17).

However, obtaining a DEXA scan on patients with epilepsy may be particularly difficult when the patient has cognitive impairment, resides in a long-term care facility, and has limited transportation options. A cross-sectional study to determine the sensitivity and specificity of QUS in this high-risk adult patient population was performed. DEXA was used as the gold standard for comparison. QUS showed a strong correlation with DEXA for the diagnosis of low BMD in this population of adult patients with epilepsy, chronic AED use, and intellectual disability (17). Additional studies are needed in the epilepsy population before recommendations can be made regarding the use of QUS.

## TREATMENT

In the absence of long-term randomized controlled trials evaluating therapeutic options for the treatment of AED-induced bone loss, recommendations are considered to be empiric. Currently, no guidelines exist regarding the treatment of bone diseases in patients with epilepsy. In addition, there are no guidelines stating which patients should receive prophylactic treatment to prevent bone loss.

### General Care

Although the data on bone loss for any individual AED are far from definitive, patients should be counseled about the general class risk of bone loss with AED. In addition, patients should be encouraged to maintain good bone health practices that include weight-bearing exercise, exposure to sunlight, and adequate intake of calcium. In addition, they should be encouraged to avoid smoking and excessive alcohol use.

High-risk patients such as postmenopausal women, patients with limited sun exposure, nonambulatory patients, and institutionalized patients should be identified. In addition, physicians should screen for the use of other medications that may have a negative effect on bone health such as low-molecular-weight heparin, warfarin, cyclosporine, medroxyprogesterone acetate, vitamin A and synthetic retinoids, loop diuretics, proton pump inhibitors, antidepressants, and antiretroviral therapy. If osteoporosis is identified, causes for secondary osteoporosis should be excluded (see Table 36.1).

### AED Selection and Evaluation

Given that AED therapy is typically long term and often life-long, the selection of initial AED therapy should be made carefully. Selection of an AED that provides the adult or pediatric patient with optimal seizure control while minimizing side effects, such as bone loss, should be the goal.

If patients have sustained a low-intensity fracture or have a DEXA T-score less than -2.5 their AED regimen should be evaluated and possibly changed. If the patient

is taking an enzyme-inducing AED or VPA, changing to another AED may be necessary. This risk of loss of seizure control must be weighed against the risk of development of osteoporosis and fractures (2). There are no guidelines that assist neurologists in this decision process. The decision to change a patient's AED regimen when a DEXA T-score is between -1 and -2.5 should be discussed with the patient.

### Calcium Supplementation

No guidelines have been published regarding calcium supplementation in patients with epilepsy taking AEDs. Since calcium supplementation is inexpensive and feasible, it is reasonable to offer 1 to 1.5 gm/day of calcium supplementation to all patients taking AEDs. Patients with increased risk factors for bone loss and/or documented low BMD on DEXA scanning should be encouraged to take daily calcium supplementation (3). For most patients, calcium carbonate taken with meals is a reasonable and inexpensive treatment option. Calcium carbonate requires an acid environment for adequate absorption. Therefore, calcium citrate should be used instead if the patient is also taking a proton pump inhibitor, since calcium citrate does not require an acid environment for absorption.

### Vitamin D Supplementation

Given that vitamin D levels are reduced in many epilepsy patients taking AEDs, numerous studies have suggested the use of daily vitamin D prophylaxis for all epilepsy patients. Higher than usual doses of vitamin D may be necessary for the epilepsy patient population since AEDs may increase the metabolism of vitamin D. The ideal dose of vitamin D is unknown. A randomized double-blind trial compared low-dose vitamin D (400 IU/daily) for adults and children with epilepsy with high dose (4,000 IU/day for adults and 2,000 IU/day for children) vitamin D supplementation. After 1 year, there was an increase in BMD in patients receiving high-dose supplementation but not for those receiving low-dose vitamin D (6). A dose of 800 to 1,000 IU/day of vitamin D is a reasonable prophylactic treatment option for all patients with epilepsy taking AEDs (3). The general guidelines for any patient with documented vitamin D deficiency ( $<20$  ng/mL or  $<50$  nmol/L) are to treat with 50,000 units of vitamin D2 or D3 orally once per week for 6 to 8 weeks, followed by maintenance dosing. Maintenance dosing is typically around 800 units of vitamin D daily (16).

There are many preparations of vitamin D available over the counter. The two most available forms are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). A randomized trial showed that cholecalciferol increased 25OHD levels more efficiently than ergocalciferol. Therefore, many authors suggest treatment with cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2) (16).

### Other Treatment Options

In the general population, it is recommended that patients with documented osteoporosis receive a pharmacological agent in addition to calcium and vitamin D. Typically, oral or intravenous bisphosphonates are used as first-line therapy. Additional therapeutic options include selective estrogen receptor modulators, estrogen/progestin therapy, parathyroid hormone, denosumab (humanized monoclonal antibody against RANKL that reduces osteoclastogenesis), strontium ranelate, calcitonin, calcitriol, and many more. Discussion of these medications is outside the scope of this chapter. Of note, hormone replacement therapy may lead to an increase in seizure activity and the risks and benefits of this therapy must be weighed before initiation.

### Surveillance

For the general population with documented vitamin D deficiency, regular screening of vitamin D levels is performed about 3 to 4 months after initiation of maintenance therapy to assess treatment status. There are no additional recommendations for further monitoring of vitamin D levels.

Given that patients with epilepsy taking AEDs have a higher risk for bone loss than the general population, it has been recommended that laboratory screening should occur at baseline and then every 6 to 12 months with monitoring of serum calcium, phosphate, alkaline phosphatase, PTH, and 25OHD. DEXA scanning has been suggested every 1 to 2 years for high-risk epilepsy patients, after 2 years of AED treatment if they only have one other risk factor for bone loss, and after 5 years of AED treatment if no other risk factors for bone loss are identified (3). For patients with low BMD on DEXA scanning, regular DEXA screening should occur every 12 to 18 months (3). Patients with abnormal lab values and multiple risk factors for osteoporosis or low BMD on DEXA should be referred to an endocrinologist. Patients with a DEXA T-score of -1 or higher do not need repeated DEXA screening as long as there has not been a change in that patient's risk factors.

It is not clear if it is beneficial for children to undergo DEXA scanning before peak bone mass is reached (young adulthood). DEXA scanning may be considered in the pediatric patient population if multiple risk factors for bone loss are identified (3).

There is accumulating evidence that patients with epilepsy taking AEDs are at an increased risk for the development of bone loss and fragility fractures. Although enzyme-inducing AEDs seem to consistently have the highest incidence of bone loss, non-enzyme-inducing AED have also been implicated in placing patients at risk for bone loss.



Further data are needed regarding AED-induced bone loss, especially with newer AEDs. The cause of bone loss in these patients has not been clearly identified, but there is ongoing research to identify the exact mechanisms. Evidence also shows that patients with epilepsy have a high rate of fractures. The cause of fractures in epilepsy patients is only partially explained by the high rate of bone loss. Other factors likely play a role in fractures, such as seizure-related injuries and falls related to medication side effects. Given that epilepsy affects 50 million people worldwide, the costs associated with fractures in this patient group is tremendous. Although suggestions have been made pertaining to the screening and treatment of bone loss in epilepsy patients, further research is needed to establish how to best manage bone loss in these patients.

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# Psychogenic Nonepileptic Events

*Jonathan J. Halford*

Nonepileptic events (NEEs) are episodes of altered movement, sensation, or experience resembling epileptic seizures which are not associated with ictal epileptiform discharges in the brain, but which, instead, have a psychological origin (1). NEEs are listed in most diagnostic manuals (2) as a dissociative or somatoform disorder, meaning that it is considered to be an involuntary response to emotional, physical, or social distress. NEE disorder is the most common type of nonepilepsy paroxysmal disorder and 20% to 40% of patients with a diagnosis of presumed epilepsy have NEEs (3–5). NEEs occur more frequently in women (accounting for 80% of cases) and the majority of patients are 15 to 35 years of age (6). Most experts in the United States use the term NEEs to describe the condition since the terms “pseudoseizures” or “spells” have pejorative connotations (7). There is also an ongoing debate as to whether the condition should be termed psychogenic nonepileptic “seizures” versus “attacks” or “events” because of the concern that the use of the term “seizure” may confuse some physicians into thinking that patients with NEEs have epilepsy (8,9).

Studies have shown that the diagnosis of NEEs are delayed by a mean of more than 7 years and that most patients are initially thought to have epilepsy (10). This leads to treatment with antiepileptic medications, which are expensive and may exacerbate NEEs (11) and sometimes the performance of expensive unnecessary procedures such as vagus nerve stimulator implantation (12). This delay in diagnosis also leads to the performance of unnecessary lab tests and diagnostic procedures and to a delay in the initiation of appropriate treatment. The patient may also be subjected to complications from invasive procedures if they present to an emergency department (ED) with a continuous NEE (“nonepileptic psychogenic status”) (13). Early diagnosis of NEEs can lower out-of-pocket and systemwide costs by reducing the need for ED visits, hospitalizations, repeated diagnostic testing, and antiepileptic medications (14). Since many of the patients with undiagnosed NEEs are initially thought to have epilepsy, it is important to consider video EEG (vEEG) monitoring for any patient having seizures which have not responded to an adequate trial of two or more antiepileptic medications.

## DIAGNOSTIC EVALUATION

NEEs may be suspected in the clinic on the basis of the patient history. There are several aspects of clinical history that hint that a patient may have NEEs, but the sensitivity and specificity of these clues for predicting whether a patient has NEEs, taken together, are not known. These clues include triggers for the events such as “stress” and “getting upset,” circumstances of the events such as the occurrence in a physician’s office, and features of the past medical history including a history of fibromyalgia or unexplained “chronic pain” (15). A florid review of systems (16) and a long list of medical allergies also suggest NEEs (17). On the other hand, a history of tongue biting suggests epileptic seizures (18).

There are several aspects of patient history that may be misleading. First, it is not uncommon for a patient with NEEs to have a history of EEGs that have been interpreted as showing evidence of epilepsy. This is usually due to the misinterpretation of normal EEGs by general neurologists in private practice who lack fellowship training in clinical neurophysiology (19). So a history of an abnormal EEG performed at an outside institution should not be taken as evidence of epilepsy. Although this is difficult to accomplish, an effort should be made to acquire and review this EEG recording to determine if it is indeed abnormal. Secondly, a history of head trauma is not helpful in making the distinction between NEEs and epilepsy in Veterans (20), and this is probably true in non-Veterans as well (although it has not yet been studied). Third, although there are characteristics to the movements of patients during a nonepileptic seizure that can help distinguish these events from epileptic seizures (if the event is recorded on video), a recent study found that these movement characteristics are not reliably reported by nonmedical eye-witnesses (21). So descriptions of patient movements during seizure by family and friends should be interpreted with caution.

Although inpatient vEEG monitoring is expensive and time consuming, it is the only reliable method for making the diagnosis of NEEs (22). Even with a vEEG recording,

distinguishing NEEs from certain types of epilepsy, such as frontal lobe epilepsy, can be difficult and even academic experts do not completely agree on all cases (23). vEEG not only provides a definitive diagnosis in almost 90% of patients but also results in treatment change in 79% of patients (24). Without vEEG monitoring, the neurologist's ability to differentiate epileptic seizures from NEEs by patient history has a specificity of only 50% (25).

There are many semiological features on video that strongly suggest NEEs. Patients with NEEs frequently close their eyes during a seizure compared to patients with epileptic seizures who usually do not close their eyes at all or for only a few seconds (26). Resistance to the eyes being pulled open by the examiner ("forced eye closure") is a characteristic of nonepileptic seizures (27). Patients frequently cry during nonepileptic seizures (28), particularly women (29). Ictal stuttering and postictal whispering voice strongly suggest NEEs (30,31). Speech during NEEs tends to contain more emotion than speech during an epileptic seizure, which tends to be more monotone (32). The speech of patients in NEEs is often intelligible and sometimes patients answer questions during nonepileptic events. The speech of patients during epileptic seizures is more often fragmented and composed of meaningless phrases or sounds (32). The patient's mouth is often open during the tonic-clonic phase of a convulsive epileptic seizure but it is usually closed during a psychogenic seizure (33).

The movements in nonepileptic events are often out-of-phase or side-to-side movements and are often chaotic disorganized thrashing (34). Out-of-phase movements are nonsynchronous among the extremities and/or oriented in multiple directions. The movements in frontal lobe seizures, the most common type of seizure confused with NEEs, often involve vocalization and quick tonic posturing (35). The movements in nonepileptic events tend to wax and wane (or completely stop and return again shortly) and to be less stereotyped than epileptic seizures. Nonepileptic events tend to last longer than epileptic seizures. The classic temporal lobe complex partial seizure lasts 10 to 140 seconds (36), whereas nonepileptic events have been documented to last 20 to 805 seconds (34).

Certain postictal behaviors are more associated with one type of event or another. Patients with NEEs often recover quickly after a seizure is over. This can happen with frontal lobe seizures as well, but it is unusual (32). Certain movements are more common after an event in epileptic seizures such as postictal nose rubbing, postictal cough (37), or noisy and stertorous (snoring or gasping) breathing (38). Postictal confusion is frequently seen after both epileptic seizures and NEEs (39), but patients with NEEs more frequently recall what happened during the event (40,41). Postictal headache and fatigue have been reported to be more common with epileptic seizures (42). Refractory interictal headache and other pain syndromes are more common in patients with NEEs (43).

There are several common misconceptions about movements in nonepileptic events. First, pelvic thrusting was

once thought to be more common in nonepileptic events, but studies have found that pelvic thrusting is as common in frontal lobe epilepsy as it is in NEE disorder (44). Second, it is also commonly believed that, unlike patients with epilepsy, patients with NEEs do not injure themselves during their seizures. But research shows that more than 50% of patients with NEE disorder have sustained an injury due to their events (45). The type of injury is helpful in differentiating epileptic seizures from NEEs. Excoriations on long bones surfaces, such as the arm, leg, or cheek, are seen in NEEs as opposed to lacerations from epileptic seizures (46). Tongue biting and incontinence were once thought to be specific to epilepsy, but they are reported by up to two-thirds of patients with NEEs (47). Tongue bites are often located laterally in patients with epileptic seizures, whereas patients with nonepileptic events bite the tip of their tongue, lip, or buccal region (26,40).

It is important to understand the limitations to vEEG monitoring in order to avoid serious diagnostic errors. Just because the ictal EEG recording is normal does not mean that the seizure event is nonepileptic. Many simple partial and frontal lobe seizures do not manifest themselves on scalp EEG (48). The ictal EEG may also be uninterpretable or difficult to read if movements generate excessive electromyographic (EMG) artifact. EMG artifact is particularly a problem with some hypermotor frontal lobe seizures. It is important to remember to ask the patient if they retained awareness during their seizure, suggesting that it may have been a simple partial seizure. Frontal lobe seizures that do not show EEG manifestations are typically brief and may involve tonic posturing or hypermotor movements (46). If a seizure occurs directly out of sleep (on vEEG monitoring), it is almost certainly an epileptic seizure, even if there is no scalp EEG manifestation. Sometimes patients with NEEs exhibit events that involve "pseudosleep" during which they appear to be asleep, but the EEG shows wakefulness (49). If a seizure is triggered by a placebo response (such as a saline injection) or by suggestion, it is probably nonepileptic.

Observing what patients bring with them to the epilepsy monitoring unit is also useful in distinguishing patients with epilepsy from those with NEEs. One study has found that patients with NEEs frequently brought a stuffed animal toy with them. In this study, 2.5% of the 834 patients (23 patients) admitted to the monitoring unit brought a stuffed animal. Of these 23 patients, 20 were diagnosed with NEE disorder and 3 with epilepsy. The three patients with epilepsy had a history of psychiatric disorder (50).

Various stimuli have been used to provoke nonepileptic events in patients undergoing inpatient vEEG monitoring. These include body part compression, verbal suggestion, placement of a tuning fork or moistened patch on the skin, intravenous administration of saline, and hypnosis (51). The use of these methods is controversial, because they may involve misleading the patient since a placebo may be used. For example, a patient may be told that they are going to be

given an intravenous medication that will bring on a seizure when they are actually being given a bolus of IV saline. This ethical concern can be avoided if the patient is completely informed of the nature of the procedure. But performing additional procedures to provoke seizures in patients with NEEs may not be necessary since photic stimulation and hyperventilation, which are typically performed every day during vEEG monitoring at most centers, frequently provokes nonepileptic seizures (52).

The use of questionnaires to predict which patients have NEEs has had some success, although no questionnaire performs perfectly. A recent study showed that a questionnaire of preictal and postictal features given to witnesses of events showed a predictive accuracy of 84% (53). The most sensitive features in the questionnaire were the presence of "postictal breathing loudness" and shorter duration of event to predict epileptic seizures. A questionnaire administered to patients showed that those with NEEs reported significantly greater levels of general awareness and responsiveness and more vivid subjective experiences during events (54). A long questionnaire assessing demographic, clinical, seizure-related, and psychological information was able to predict NEEs with a 94% sensitivity and 83% specificity at one clinic and a 85% sensitivity and a 85% specificity at another (55).

Various serum markers have been studied to attempt to differentiate NEEs from epilepsy. Serum creatine phosphokinase (CPK) concentrations measured 12 to 15 hours after generalized convulsive events, if higher than 160 mg/dl, strongly suggested epileptic seizures (56). One study showed that adults with NEEs had decreased levels of brain-derived neurotrophic factor (BDNF) in comparison to healthy controls but the levels of BDNF did not differ between patients with NEEs and epilepsy (57). An assessment by the American Academy of Neurology concluded that a serum prolactin level measured 10 to 20 minutes postictally could help differentiate convulsive epileptic seizures from a convulsive nonepileptic event (58). Overall, it appears that two measures, CPK and prolactin, are of use, but only after a generalized convulsive event.

Neuroimaging is not helpful in distinguishing patients with NEEs from those with epilepsy. Between 10% and 30% of patients with NEEs are found to have abnormalities on brain MRI. These abnormalities were usually nonspecific gliosis or postoperative defects, but mesial temporal sclerosis was found in few cases. Just because a patient has neuroimaging abnormality associated with epilepsy does not mean that they definitely have epilepsy (59,60). Most ictal SPECT scans are negative in patients with NEEs (61), but they can also be negative in patients with epilepsy, so a negative SPECT scan also does not help much in making the distinction.

### RISK FACTORS AND PATHOGENESIS

NEEs tend to occur during the second to fourth decades of life, with only up to 20% of cases occurring after the age of 40 (62). Although the cause of NEE disorder is unknown, studies find that many patients have certain types of stressors that

may lead to the disorder. Patients with NEEs are more likely to be obese than patients with epilepsy (63). In children and adolescents, difficulties at school, family discord, and cognitive dysfunction are frequently present. In adolescents, there is frequently a history of depression (64). A history of sexual abuse is very uncommon in children and adolescents (64). Adult women with NEEs also frequently report a history of sexual abuse (65). Three-quarters of patients report some type of traumatic antecedent factor such as sexual abuse (32.5%), physical abuse (26%), bereavement (18.7%), health-related trauma (8.3%), or accident or assault (8%). The stressors in these patients may not be reported initially and may be discovered only later during counseling (51). Janet first proposed the theory that traumatic memories could lead to the dissociation, or splitting off, of nuclei of consciousness, which could occasionally take over a person's behavior (without the person's conscious awareness) (66). This phenomenon was first noted in his studies of hypnotism, and it has been reported that patients with dissociative disorders tend to be easily hypnotized (67). But no method for testing this hypothesis has been developed. Although some patients with NEEs may have abnormalities on brain imaging, there is no specific neuroimaging finding associated with NEEs.

Functional imaging studies have begun to reveal areas of the brain that are involved in psychogenic movement disorders other than NEEs. A recent functional MRI (fMRI) study in patients with conversion disorder showed increased connectivity between the right amygdala and the right supplementary motor area, while subjects visualized faces with different emotions in comparison to normal controls (68). This suggested there was a "hyperlink" between brain areas regulating emotion and areas initiating motor movements. Another study showed that patients with psychogenic tremor had decreased activity in the right temporal-parietal junction in comparison to patients with physiologic tremor. This brain region is thought to compare internal predictions with actual events and may explain why these movements are not perceived by the patient as self-generated (69). This type of functional imaging study has probably not been performed on patients with NEEs because subjects are required to lie still while they are in the MRI scanner, which is possible for patients with ongoing psychogenic tremor but not for patients having a nonepileptic event.

### TREATMENT AND OUTCOME

The first phase of treatment is communicating the diagnosis to the patient at the end of inpatient vEEG monitoring. Most experts agree that how the diagnosis is communicated is very important to improving the chance for a good outcome (70). Research shows that when patients in the epilepsy monitoring unit are not given information on their diagnosis, they have a higher likelihood of no improvement or worsening of NEEs (71). Little research has been done on exactly how the diagnosis should be communicated to patients, but there is a study that suggests that the diagnosis should be presented in a positive light (6). The following is



a method that the author has found useful in presenting the diagnosis to patients.

I usually begin with telling the patient that “I have reviewed all of your seizures that we recorded and I have some good news for you—you don’t have epilepsy.” I go on to explain that epilepsy is a serious and often disabling disease that often does not respond to seizure medications and so they should be thankful that they do not have that. I next explain that they have a condition that we frequently see in the epilepsy monitoring unit, called “nonepileptic events,” and that it is a manifestation of stress or trauma. I explain that the stress or trauma may not have happened recently but could have happened in the distant past. I tell them that stress is manifested in different ways in different people—some people may feel nervous, sweaty, or tremble when they experience stress but others may manifest stress by having these types of “events.” Importantly, I reassure them that I don’t think that they are “crazy,” because I have learned that patients are often concerned with this. But I do explain that patients with “nonepileptic events” often have a history of physical or sexual abuse or trauma as well as other comorbid psychiatric disorders such as anxiety, depression, or posttraumatic stress disorder, which need to be treated. I tell them that they no longer need to take antiepileptic medications since these medications will not stop them from having their events “as you have noticed.” I then let the patient talk about how this news makes them feel for awhile. Often they will have questions. Usually the patient will say that this make sense and talk about past abuse or stressors. Some researchers suggest showing the patient the video recording of their seizures as part of this initial talk (6), although this is not something that I do on a routine basis, I do show the patient the vEEG of their events if they ask.

When explaining the treatment plan, it is important to tell patients that there is no single treatment or “magic bullet” that can stop their events, rather several treatments are usually employed. First, they will need to stop taking antiepileptic drugs (AEDs). This is not just because the medication is not helping but also because the medication is expensive, has potential short-term and long-term side effects, and can cause confusion in other treating physicians who are likely to assume that the patient has epilepsy because they are on an AED. A study of immediate versus delayed discontinuation of AEDs demonstrated that immediate AED withdrawal was not associated with greater risk to patients and improved outcome—patients with early discontinuation of AEDs used less rescue medication and were more likely to attribute their NEEs to their mental state at follow-up (72). Second, they will need outpatient counseling with a psychologist for at least several months. Two recent studies of cognitive behavioral therapy (CBT) in comparison to standard medical treatment have reported improvement in event freedom rates, psychiatric symptoms, quality of life, and psychosocial functioning by the end of treatment (73,74). Sometimes CBT is difficult to arrange as relatively few practitioners are able to provide this. Any type of psychotherapy for these patients is probably better than none.

In a recent survey, the majority of physicians involved in the treatment of NEEs stated that psychological treatment was the treatment of choice for these patients (75). Third, outpatient evaluation by a psychiatrist should be arranged. Psychiatric comorbidity is common in patients with NEE disorder. The types of comorbid psychiatric disorders most often present are depression, anxiety, posttraumatic stress disorder, and personality disorders (76). Treatment of these comorbidities could improve the patient’s quality of life and their NEEs. A recent pilot study of treatment of depression with sertraline in patients with NEEs showed improvement in their nonepileptic event frequency (77). Fourth, outpatient follow-up with a neurologist is important so as to communicate to the patient that they are not being cast aside once the diagnosis of NEEs is made and also to make sure that the patient has their antiepileptic medication discontinued and gets outpatient psychological counseling and psychiatric evaluation.

Outcome studies have shown that a certain percentage of patients will have their NEEs stop after the diagnosis is communicated to them. In one study, 50% of 68 patients newly presenting with NEEs were event free after 3 months and 44% after 6 months (78). Another recent study with follow-up at 6 and 12 months showed that 38% of patients were event free and 18% had increased events (79). Factors associated with poor outcome include denial of stressors and psychosocial problems, new somatic symptoms after disclosure of the diagnosis, a history of chronic abuse, and higher rates of depression and personality disorders (80). Other factors associated with poor outcome include female sex and patients drawing social security payments (79). Several studies have suggested that a longer delay to diagnosis is associated with worse outcome (45,47,81), although this was not found in the most recent outcome study (79). Although a certain percentage of patients will become event free after the diagnosis is delivered, long-term results suggest that the decrease in nonepileptic event frequency shortly after the diagnosis is not maintained longitudinally when solely giving the diagnosis is the main intervention (45,82). Therefore, patients should be offered the additional treatments described previously.

In conclusion, NEEs are common and often mistaken for epileptic seizures. Many patients with NEE disorder often receive years of incorrect, dangerous, and invasive treatment for epilepsy. Proper diagnosis starts with considering NEE disorder in the differential diagnosis of a patient presenting with spells that have not responded to medications. Certain premorbid conditions and clinical features can suggest the diagnosis, but vEEG monitoring is necessary for confirmation of NEEs. Once a diagnosis is made, communicating this effectively to a patient is critical, as is arranging appropriate treatment. CBT is the best available treatment for NEEs, but it is also important to discontinue AEDs. With appropriate therapy, many patients will be successfully treated.

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# Psychiatric Comorbidities

*Sarah K. Rivelli*

Approximately half of all patients with epilepsy have psychiatric symptoms or disorders. Psychiatric comorbidity is an important predictor of health and quality of life among patients with epilepsy and requires careful evaluation and treatment. This chapter will review psychiatric comorbidity commonly encountered among patients with epilepsy, the use of antiepileptic drugs (AEDs) in psychiatry, the risk of suicide among patients with epilepsy, adverse psychotropic effects of AEDs, and the risk of seizure associated with psychotropic medications.

## PSYCHIATRIC COMORBIDITIES

### Anxiety

Anxiety and anxiety disorders appear to be common among patients with epilepsy. The main anxiety and related disorders as classified by the *Diagnostic and Statistical Manual-5* (DSM-5) (1), and estimated prevalence in patients with epilepsy is listed in Table 38.1.

The unpredictability of seizures and their negative impact on functioning may lead to anticipatory anxiety in some patients. The areas of the brain involved in anxiety include the amygdala and hippocampus. The amygdala mediates autonomic and endocrine responses through the output to the hypothalamus and avoidance behavior through output to the periaqueductal gray matter. The hippocampus mediates the reexperiencing of fear and its affective component. Pharmacologic treatments of anxiety reduce excessive output of these neurons (2). Antiepileptic agents that potentiate GABA-ergic inhibition, such as benzodiazepines, are also effective antiepileptic agents.

### *Panic Attacks and Panic Disorder*

Interictally, patients with epilepsy have been found to have high rates of panic attacks, with up to 20% of patients having at least one panic attack. Panic attacks are characterized by an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and is associated with a variety of physiological symptoms such as shortness of breath,

chest pain, and nausea. A diagnosis of panic disorder (PD) is made if they meet DSM criteria (see Table 38.1); prevalence rates in epilepsy range between 5% and 10% (2).

Benzodiazepines and antidepressants are equally efficacious in PD, however antidepressants are considered preferable due to the risk of abuse, tolerance, withdrawal, and negative effects on cognition and motor function with benzodiazepines. Clonazepam and alprazolam are approved by the FDA for PD. Alprazolam appears to have more liability for abuse and generally should be avoided. Serotonin reuptake inhibitors (SSRIs) approved for PD include sertraline, venlafaxine, paroxetine and fluoxetine (see Table 38.2). SSRIs are better tolerated and appear to be equally efficacious to tricyclic antidepressants (TCAs) such as imipramine and clomipramine that are approved by the FDA for PD. Moreover, depression and anxiety disorders tend to be comorbid and antidepressants offer benefit for both disorders, while benzodiazepines do not. One strategy in the highly anxious distressed patient is to start both an antidepressant and a benzodiazepine simultaneously, and then taper the benzodiazepine after 4 to 6 weeks, once the antidepressant has started to take effect and a mean effective dose has been achieved. Among patients with epilepsy, a careful slow taper of benzodiazepine, such as a decrease by 10% to 20% daily, must be ensured with concurrent adequate AED treatment on board. There is some weak evidence that gabapentin may be helpful with panic, and thus it may be a useful adjunct in certain patients with seizures and comorbid panic attacks.

Cognitive behavioral therapy (CBT) is highly effective for panic disorder and as effective as pharmacotherapy. There are often challenges with access to high-quality treatment, however. When available, referral for CBT should always be made.

### *Generalized Anxiety Disorder*

Generalized anxiety disorder (GAD) may be more common among patients with epilepsy, though studies have not demonstrated this consistently (2). It is a common, yet debilitating, disorder that is frequently comorbid with depression in particular, and affects about 5% of the general population



TABLE 38.1 Anxiety and Related Disorders

DISORDER	KEY DIAGNOSTIC FEATURES	ESTIMATED PREVALENCE IN EPILEPSY
Panic disorder	Recurring panic attacks Worry about attacks and/or maladaptive behavior May be accompanied by agoraphobia (fear of public places) At least four associated physical or psychological symptoms: palpitations, sweating, trembling, shortness of breath, feelings of choking, chest pain, nausea or abdominal distress, feeling dizzy or faint, chills or hot, paresthesias, derealization or depersonalization, fear of losing control, "going crazy" or dying.	5% to 10%; up to 20% with isolated panic attacks
Generalized Anxiety Disorder	Excessive anxiety and worry about a number of issues for at least 6 months At least three of six associated symptoms: Restlessness or keyed up, easily fatigued, difficulty concentrating, irritability, muscle tension, insomnia or restless sleep.	3% to 12%
Social anxiety Disorder	Marked fear or anxiety about one or more social situations The social situations almost always provoke anxiety Avoidance of social situations Lasts at least 6 months	3% to 7%
Posttraumatic Stress Disorder	Exposure to actual or threatened death, serious injury, or sexual violence Symptoms last at least for 1 month and include:  Intrusive recollections, distressing dreams, flashbacks, psychological or physical distress at exposure to internal or external cues related to trauma Persistent avoidance of stimuli associated with the traumatic event Negative alterations in cognitions and mood associated with the traumatic event Marked alterations in arousal and reactivity associated with the traumatic event(s), such as irritable behavior and angry outbursts, reckless or self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, sleep disturbance	1%
Obsessive Compulsive Disorder	Obsessions – recurrent thoughts, urges, images that are intrusive and unwanted; attempts to neutralize or suppress  Compulsions – repetitive behaviors or mental acts in response to obsessions that are time-consuming and cause impairment	1% to 5%

in the United States. SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), and TCAs all have proven efficacy in GAD. FDA-approved treatments include sertraline, escitalopram, paroxetine, venlafaxine, and duloxetine (see Table 38.2).

Buspirone is a 5 hydroxytryptamine 1A receptor (5HT<sub>1A</sub>) partial receptor agonist, which is thought to lead to its anxiolytic effects. It has been found to be as effective as diazepam in treating GAD; however, it takes up to 6 weeks at a total daily dose of at least 30 to 45 mg (given in two to three divided doses) for full effect. Benefits of buspirone include that it is nonsedating with no risk for abuse or dependence and does not lead to withdrawal symptoms or seizures when discontinued. On the other hand, patients and providers tend to abandon the treatment prior to achieving benefit due to the delay in noticeable effect. Carbamazepine and other CYP3A4 inducers tend to lower the effective level of buspirone, and thus titration to maximal dose of 20 mg three times daily may be required.

Hydroxyzine has been found to be significantly more efficacious than placebo in treating GAD and is low cost. However, it causes sedation, which can be undesirable among patients already taking an anticonvulsant with such side effects. Quetiapine is effective in treating GAD according to a few randomized controlled trials (RCT); however, its negative impact on glucose and lipid metabolism, risk for tardive dyskinesia (TD), and tendency to cause orthostatic hypotension suggest that other agents are preferable for the treatment of GAD.

Pregabalin is the anticonvulsant agent with the strongest evidence for treating GAD, with demonstrated efficacy in short-term and longer-term trials (3). It is approved in Europe for the treatment of GAD. The effect size of pregabalin in treating GAD appears to be at least as large as that for SNRIs, and pregabalin may be better tolerated. Thus, pregabalin is the first-line anticonvulsant for a patient with comorbid epilepsy and GAD.

**TABLE 38.2 Nontricyclic Antidepressants**

NAME	CLASS	STARTING DOSE	MAXIMUM DOSE	PRIMARY PSYCHIATRIC INDICATIONS	ISSUES
Citalopram	SSRI	20 mg	40 mg	Depression	Dose dependent QTc prolongation, avoid >20 mg in elderly
Escitalopram	SSRI	10 mg	20 mg	Depression, panic, GAD	Cost
Fluoxetine	SSRI	20 mg	60 mg	Depression, panic	Long half-life, inhibits CYP2D6, CYP3A4, CYP2C9, CYP2C19; increases phenytoin and possibly carbamazepine levels
Fluvoxamine	SSRI	50 mg	300 mg	OCD, depression, panic, GAD	Potent drug interactions due to inhibition of CYP3A4, CYP2C19, CYP2C9; marked increases in phenytoin levels
Paroxetine	SSRI	10–20mg	40 mg	Depression, panic, GAD	Anticholinergic, CYP2D6 inhibitor, prominent sexual adverse effects
Sertraline	SSRI	25–50 mg	200 mg	Depression, panic	Safe in patients with acute coronary syndrome and heart failure
Desvenlafaxine	SNRI	50 mg	50 mg	Depression	Cost
Duloxetine	SNRI	30 mg	120 mg	Depression, GAD	Cost, constipation, also effective in fibromyalgia and diabetic neuropathy
Venlafaxine	SNRI	37.5 mg	300 mg	Depression, panic, GAD	Mild increase in diastolic blood pressure
Mirtazapine	Alpha-2 antagonist	15 mg	45 mg	Depression	Sedation, weight gain, low risk of sexual adverse effects
Bupropion SR	NDRI	150 mg	450 mg	Depression, smoking cessation	Lowers seizure threshold, not effective in anxiety
Trazodone	5HT antagonist and SSRI	50 mg (insomnia) 150 mg (depression)	150 mg (insomnia) 400 mg (depression)	Insomnia, depression	Sedation, orthostatic hypotension, rare priapism
Vilazodone	5HT antagonist and SSRI	10 mg	40 mg	Depression	Cost

### *Social Anxiety Disorder*

Social anxiety disorder is characterized by extreme fear of social situations, leading to avoidance behavior that significantly impairs function. It appears to be equally prevalent among patients with and without epilepsy, at about 7% (2). SSRIs appear to all be equally efficacious, with high-quality evidence for escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. Low-quality evidence suggests that gabapentin and pregabalin are effective in treating social anxiety disorder, and these may certainly be useful approaches among patients with epilepsy.

### *Posttraumatic Stress Disorder*

Posttraumatic stress disorder (PTSD) comprises a diverse group of symptoms beyond anxiety that include intrusive recollections, avoidance of stimuli associated with the traumatic event, marked arousal and reactivity, and negative cognitions and mood (see Table 38.1). Thus, treatment of

this disorder tends to be complex and dependent on which symptom clusters are most debilitating. SSRIs are often considered first-line treatments with decent evidence in favor of paroxetine and sertraline, which are FDA approved for this indication.

Studies examining anticonvulsants have largely been negative, such as well-designed trials of lamotrigine and topiramate that did not demonstrate significant symptom improvement (2). Second-generation antipsychotics such as risperidone and quetiapine may be useful adjuncts to SSRIs in some patients with PTSD, but adverse metabolic effects and risk for TD argue for other treatment approaches whenever possible.

PTSD-specific CBT has consistently been shown to be efficacious in PTSD and generally includes elements of desensitization and exposure. Eye movement desensitization and reprocessing (EMDR) is an effective, though somewhat controversial, treatment for PTSD. It has been shown to be as effective as CBT and is recommended by the American

Psychiatric Association, among others, for the treatment of PTSD. EMDR's impact likely comes from elements of exposure therapy, and the eye movements are actually irrelevant to its efficacy. Thus, if available, referral to EMDR is certainly reasonable because of its structured, manual-based approach that comprises desensitization and exposure, with proven efficacy in PTSD. Finally, given the complexity of the constellation of symptoms in PTSD, it is recommended that such patients generally receive specialty mental health care and referral is recommended.

### *Obsessive Compulsive Disorder*

Obsessive compulsive disorder (OCD) tends to be among the most disabling psychiatric disorders and requires specialty treatment that includes psychotherapy, such as CBT or exposure therapy, and pharmacotherapy. OCD is characterized by the presence of recurrent intrusive thoughts, recollections, or images that are unwanted and distressing (obsessions) accompanied by repetitive behavior or mental acts in response to obsessions that are time consuming and impair functioning (Table 38.1). High-dose SSRIs appear to be required in treating OCD, which may increase seizure risk (2). FDA-approved agents for OCD include fluvoxamine, paroxetine, and sertraline (Table 38.2). Fluvoxamine is an SSRI that appears to have only modest efficacy in treating depression, but is helpful in OCD in particular. The use of fluvoxamine is confounded by pharmacodynamic interactions due to inhibition of CYP1A2 which also metabolizes tizanidine, and CYP2C19, which metabolizes diazepam and phenytoin.

Clomipramine is a highly serotonergic TCA which is the most effective agent in treating OCD and appears to have more effect than SSRIs. However, it is associated with a higher proconvulsant risk, may cause cardiac conduction delay, has more anticholinergic side effects and leads to weight gain, thereby limiting its use. Lamotrigine is one anticonvulsant that may be helpful in OCD; low quality evidence suggests that it may be an effective augmentation strategy for patients that fail to respond adequately to SSRIs. Patients with OCD will likely be referred to specialty mental health care, particularly for CBT which is the mainstay of treatment.

## **Depression**

### *Prevalence and Clinical Presentation*

The prevalence of active depression among people with epilepsy has been estimated at 23%, and lifetime prevalence at 13% in community-based samples (4). People with epilepsy have at least a twofold increased odds of having depression (5). Depression assessed by a self-report screening questionnaire, the Patient Health Questionnaire (PHQ-9), was found in 29.3% of patients presenting to an epilepsy clinic (6).

Depression is one of the main determinants of low health-related quality of life (HRQOL) in epilepsy, and subsyndromal and major depression appear to have an

equally negative impact on HRQOL (7). Of note, patients with well-controlled seizures tend to have lower depression scores than those with persistent seizures in various studies. Depression is chronic in about half of patients, with atypical features being more common among those with epilepsy. Atypical features include predominant irritability, anxiety, and hypersomnia. Anxiety disorders are frequently comorbid, occurring in about half of all patients with depression. Symptoms of depression include a persistently sad or low mood, loss of pleasure in activities, decreased or increased appetite and/or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished concentration, recurrent thoughts of death and/or suicidal ideation. The diagnosis of depressive disorder is given when symptoms persist nearly every day for most of the day over a 2-week period (1).

Transient depressed mood may occur preictally, periictally, or postictally. Interictal dysphoric disorder tends to be chronic and includes labile mood, depressive and irritable symptoms, and appears distinct from depressive disorder and generally improves with improved seizure control. In fact, complete seizure control appears to reduce the risk for depression overall. Postictal depression has been found to occur in 43% of patients with poorly controlled epilepsy (6).

### *Differential Diagnosis*

Important in the differential diagnosis is considering the impact of AEDs on mood, including the negative psychotropic effects of some AEDs that cause fatigue, lethargy, and cognitive slowing and may be mistaken for depression. One approach is to avoid the use of AEDs with negative psychotropic properties among patients who appear at increased risk for mood disorders, such as those with a positive personal or family history. Agents thought to increase the risk of developing depression include benzodiazepines, barbiturates, tiagabine, vigabatrin, topiramate, zonisamide, and levetiracetam (8). This relationship with depression is likely more related to sedating effects and cognitive slowing from these agents than an increase in sadness or loss of pleasure seen in depression per se, though dysphoria has been described with topiramate and levetiracetam in particular. Also of note, AEDs such as carbamazepine, phenytoin, and primidone may decrease the serum level of antidepressant medications via CYP induction, leading to a relapse in depression in patients who had previously responded to treatment with an antidepressant (5). Finally, patients undergoing epilepsy surgery appear at increased risk for depression, with 20% to 30% having a depressive episode in the first 6 months postsurgery (5).

### *Underlying Mechanisms*

There are likely many mechanisms at play in the association between epilepsy and depression. One factor is that epilepsy is a stressor, particularly because seizures are unpredictable and debilitating and often negatively impact social

functioning, leading to learned helplessness and reduced concept of self-efficacy, all of which may lead to depression. Epilepsy can be a burden to patients due to stigma, disability, and the need to restrict activities such as driving or swimming and may contribute to the development of depression. AEDs may also facilitate the development of depression or lead to symptoms such as fatigue and cognitive slowing and exacerbate depression. Examination of clinical factors in epilepsy has not yielded any consistent relationships between epilepsy duration, focus site, or lateralization, except for some evidence suggesting that complex partial seizures are more common among patients with depression and epilepsy compared to those with epilepsy alone (7).

### *Treatment*

There have been virtually no randomized controlled trials evaluating the treatment of depression among patients with epilepsy, and thus treatment is based on data from studies of the general population of depressed patients (5). SSRIs (Table 38.2) are considered first-line therapy and are all equally efficacious in treating depression (5). Bupropion is generally avoided in patients with epilepsy due to its pro-convulsant effect.

Before starting treatment with an antidepressant, ensuring that there is no personal or family history of mania or hypomania is important, as antidepressant treatment can provoke a switch into mania and is associated with more frequent episodes of bipolar disorder, called rapid-cycling bipolar disorder. Mania is characterized by a period of persistently elevated, expansive, or irritable mood lasting at least 1 week and accompanied by inflated self-esteem, decreased need for sleep, excessive talking that is often pressured, racing thoughts, distractibility, increased goal-directed activity, or psychomotor agitation (1). Hypomania is characterized by a shorter duration of only 4 days and symptoms tend to be less severe. Referral to a psychiatrist may be warranted to clarify diagnosis or to manage severe manic symptoms.

Treatment of depression should include titration up to a maximal dose of an antidepressant in order to achieve full response, and a trial at the effective dose for at least 6 weeks prior to switching therapies or declaring treatment failure. If a patient fails to have remission of the majority of symptoms after two adequate trials of an antidepressant, referral to a psychiatrist is certainly warranted. Note that changes or initiation of AEDs may reduce serum levels of antidepressants, and thus high doses of antidepressants may be required. Inducers of CYP3A4 such as phenytoin, carbamazepine, and phenobarbital and high-dose oxcarbamazepine and topiramate may reduce serum levels of SSRIs, requiring an increase in dose by as much as 25% to 30% to maintain antidepressant efficacy.

Adverse effects of SSRIs include restlessness and nausea, which tends to be transient. Sexual disturbances are common, which include decreased libido and delayed or absent orgasm; paroxetine appears to have the highest propensity to cause such effects, while citalopram, escitalopram,

and mirtazapine much less so. SSRIs are also associated with increased risk of osteoporosis and doubling of fragility fracture risk, and thus careful attention to bone density is needed for patients who are also taking high-osteoporotic-risk AEDs such as phenytoin.

### *Psychotherapy*

A number of psychotherapies have been shown to be effective in treating depression in high-quality RCT. CBT has specifically been shown to be efficacious among patients with depression and epilepsy and might be considered first line for such patients, particularly if anxiety is also present. Some data suggest that CBT among adolescents with epilepsy may prevent the development of depression, and may help with patients coping with epilepsy as a chronic condition.

### *Referral*

Referral to a psychiatrist is warranted for refractory depressive episodes, diagnostic clarification, psychotic symptoms, severe mania, and concern for suicide risk.

### *Somatic Therapies*

Electroconvulsive therapy (ECT) is a highly effective treatment for depression, leading to rapid treatment response and benefit in refractory patients and those with psychosis or catatonia. ECT has also been used in rare instances to treat refractory status epilepticus since it increases the seizure threshold over time. Limitations to ECT include lack of focal stimulation, negative cognitive effects such as anterograde amnesia, stigma, lack of access, and the need for general anesthesia. Vagal nerve stimulation (VNS) is approved both for treatment-resistant depression and refractory epilepsy. Mood improvement has been demonstrated among patients receiving VNS for epilepsy and it may be a viable treatment for patients with comorbid depression and epilepsy (7).

Repetitive transcranial magnetic stimulation (rTMS) involves stimulating superficial nerves in the brain by placing a magnetic coil near the skull that creates a magnetic field. Low-frequency stimulation leads to decreased excitability, while high-frequency stimulation increases excitability of targeted regions. In depression, rTMS is used to increase excitability of the left prefrontal dorsal cortex with well-demonstrated improvement in mood. rTMS is approved for the treatment of depression, but does not appear to be as potent a treatment as ECT, its role may be reserved for less refractory patients. Low-frequency stimulation, on the other hand, has been examined to decrease activity of epilepsy foci, but so far has generally produced negative results. It is currently unclear if rTMS might prove useful among patients with epilepsy and depression. Seizures provoked by rTMS have been virtually unknown since the establishment of safety guidelines in the mid-1990s, but a small increased risk of seizure has been reported among patients with epilepsy receiving high-frequency rTMS that ranges from 0% to 3.6%.



## Psychosis

Psychosis occurs in as many as 9% to 10% of patients with epilepsy. Psychosis may be seen in ictal, periictal, and postictal phases of epilepsy. Bitemporal seizure focus and seizure cluster are documented risk factors for psychosis in epilepsy (9). Persistent psychosis may arise from complex partial status due to activity in the limbic and/or frontal lobes and appear very similar to that of primary psychosis clinically (10). Distinguishing features that favor epilepsy include confusion, inattention, and/or altered consciousness. Some so-called interictal psychosis may actually be due to subclinical epileptic discharges and appears to occur predominantly in temporal lobe epilepsy, while clinically it is often indistinguishable from primary psychosis (10).

There is some evidence that seizures and psychosis might be antagonistic or reciprocal, at least in some patients. This antagonism is demonstrated by “false normalization,” which is the paradoxical normalization of the EEG during an increase in psychotic symptoms. Similarly, it has been observed that for some patients, when they are more psychotic, they have fewer seizures (9).

Psychotic symptoms in epilepsy most typically include hallucinations and delusions; aura may also be present. Other symptoms such as persistent thought disorganization, impaired social functioning, or bizarre behavior are less common among patients with psychosis in epilepsy. On the other hand, neuropsychological testing comparing patients with epilepsy and those with schizophrenia did not show significant differences in cognitive profiles (9). Most experts agree that the most common substrate for psychosis in epilepsy is limbic seizure activity, but this is not specific, nor sufficient, for the production of symptoms that may vary widely and include sensory phenomena as well. Postictal psychosis tends to follow recurrent seizures generally after a lucid interval of 24 to 48 hours and is generally time limited, resolving within 2 weeks.

Though hallucinations, illusions, and delusions might suggest different clinical diagnoses in psychiatry, there is less evidence for distinct areas or networks in the brain being responsible for such symptoms (11). In fact, stimulation of the same area even within the same individual can produce widely different clinical symptoms, while stimulation of different areas can produce similar phenomena, which suggests widely distributed neuronal networks as the basis for such phenomena (11).

## Aggression

Some patients have episodes of aggression that are clearly linked to seizure activity and improve with seizure control. Such a diagnosis is made preferably with video EEG (vEEG) recording, documenting seizure during aggression. The aggressive behavior seen in epilepsy tends to be poorly organized, less purposeful, and of brief duration. Though not definitive, seizures presenting as aggression are thought

to arise from the amygdala and limbic structures (9). AEDs that might be particularly helpful for such patients include those that are used for mania and aggression in psychiatry, namely, valproate and carbamazepine. Aggression occurring only in the interictal period may be more related to underlying psychiatric disorders such as mood disorders or personality disorders (9).

## Attention-Deficit Hyperactivity Disorder

Attention-deficit hyperactivity disorder (ADHD) has been found to be more common among patients with epilepsy, with an estimated prevalence among children with epilepsy of 14%, while patients with ADHD have about 2.5-fold risk of developing epilepsy (9). Overall, adequate treatment with AEDs appears to improve attention among these patients. Treatment with stimulants, such as methylphenidate, appears to be safe in patients with ADHD and epilepsy. EEG abnormalities that have been well documented in ADHD include increased fronto-central theta band activity and increased theta/beta power ratio during rest compared to controls. Significant heterogeneity is noted among patients with ADHD, however, and the role of EEG in diagnosis or monitoring has not yet been elucidated.

## SUICIDE RISK, EPILEPSY, AND ANTIEPILEPTIC DRUGS

Patients with epilepsy report a high lifetime prevalence of suicidal thoughts, plans, and attempts and have a three- to fourfold increased risk for suicide (8). Among patients having epilepsy and known psychiatric disorder, the risk climbs to a 13-fold increased risk (8). The period immediately following a diagnosis of epilepsy is a particularly vulnerable period; if a psychiatric condition is also present, the risk is almost 30 times higher than the general population (8). Patients with temporal lobe epilepsy also appear to be at elevated risk. Another vulnerable group is patients undergoing epilepsy surgery, where the risk for mood disorders is highest in the first 3 months postsurgery and confers increased risk for self-harm (9).

Examination of suicide risk due to AEDs has been confounded by the low frequency of suicide; retrospective analyses; combining studies of AEDs with widely varying mechanisms; combining studies where AEDs are prescribed for pain, epilepsy, psychiatric, and other indications together; and lack of adjustment for known risk factors for suicide such as depression or prior suicidality. Suicidal thoughts and behaviors were not assessed systematically in studies a priori, but were captured when coded as adverse events in the studies. Moreover, it is difficult to build a case for harm without evidence of reasonable potential mechanisms by which the agents might lead to such risk, which is impossible given the diverse pharmacologic agents grouped together for analyses and that epilepsy trials often allowed polytherapy.

In 2008, the FDA requested that AED labeling include a warning regarding risks of suicidal thoughts and behavior.

At that time, the FDA reported on a meta-analysis that included studies of 11 different AEDs prescribed to 43,892 patients for epilepsy, psychiatric disorders, pain disorders including fibromyalgia and migraine, and other conditions (see Reference 12 for review). The analysis showed an increased risk for suicidal thoughts or behaviors among patients randomized to AEDs versus placebo (0.43% vs. 0.24%, respectively; OR 1.80 [1.2–2.7]). Analysis of the epilepsy subgroup of patients alone gave an OR of 3.53 (1.28–12.10), with a wide confidence interval suggesting an imprecise, but statistically significant estimate. Examination of the psychiatric, pain, and other indication studies yielded nonstatistically significant increased odds of suicide among patients randomized to AEDs. Only topiramate and lamotrigine yielded statistically significant increased odds of suicidal thoughts and behavior when AEDs were examined separately (OR 2.53 [1.21–5.85] and OR 2.08 [1.03–4.40], respectively). On the other hand, carbamazepine appeared to have a protective effect on suicidality with an OR of 0.66. Thus, a class effect appears unlikely despite the call for labeling regarding increased risk of suicide with AEDs as a class.

Interestingly, naturalistic studies have not supported an increased risk of suicide associated with AEDs among patients with epilepsy, and the literature includes contradictory results (12). There is some signal in the literature that lamotrigine, topiramate, and, to a lesser degree, levetiracetam are associated with an increased risk for suicidal thoughts or behavior, but this needs to be more thoroughly examined in prospective trials with careful assessment for risk factors and the occurrence of suicidality.

People with epilepsy are more likely to have depression and other psychiatric comorbidities, and thus are at increased risk for suicide, and some AEDs may increase this risk further. However, this should not prevent adequate treatment of epilepsy, but argues for careful psychosocial assessment and close monitoring and follow-up. Assessment of risk factors for suicide should be considered, which include personal or family history of suicidal behavior, mood disorders, hopelessness, substance abuse, social isolation, and access to lethal methods, such as guns. Patients with suicidal ideation should be referred for mental health evaluation; the urgency of this depends on the severity of symptoms. For any patient presenting with suicidal ideation and severe depression, hopelessness, psychosis, and/or poor psychosocial support an emergency evaluation is generally warranted.

There may be an increased relative risk of suicide with some AEDs, but the absolute risk is small given that suicidality is actually not that common. Balancing this risk against the much more likely and immediate risk of untreated epilepsy, it becomes obvious that there is more benefit than harm in the adequate treatment of epilepsy with an AED.

## ANTIEPILEPTIC DRUGS IN PSYCHIATRY

AEDs are frequently used in psychiatry, particularly to treat bipolar disorder. In fact, the majority of AED prescriptions (up to about 70%) are written for off-label uses,

including psychiatric conditions and pain disorders (8). For patients with epilepsy and a comorbid psychiatric condition, treatment with an anticonvulsant with potentially beneficial psychiatric properties should be considered. On the other hand, attention to the adverse psychotropic effects of AEDs needs to be considered, particularly in more vulnerable patients with personal or family histories of psychiatric disorders. AEDs used in psychiatry are shown in Table 38.3; adverse psychotropic effects are shown in Table 38.4.

### Barbiturates

Barbiturates are known to cause sedation, yet also paradoxical irritability and impulsivity in children and the elderly. Barbiturates have also been associated with depression and suicidal ideation in patients with a positive family history of depression. Barbiturates can lead to dependence, abuse, and withdrawal. In the past, barbiturates have been used to treat alcohol and sedative-hypnotic withdrawal, yet because of the risk of respiratory depression, other agents tend to be preferred.

### Phenytoin

Phenytoin is another older agent with a negative psychotropic side effect profile; it is associated with sedation, cognitive slowing, psychosis, and encephalopathy. It does not appear to have a beneficial role in psychiatric disorders; small low-quality trials have shown benefit in reducing impulsivity and aggression.

### Benzodiazepines

Benzodiazepines are frequently prescribed for anxiety and insomnia and have a role in the short term and acute treatment of these conditions. However, benzodiazepines lead to sedation, cognitive slowing, amnesia, ataxia, tolerance, and, at times, abuse, thereby limiting their utility. Benzodiazepines may also cause paradoxical irritability and disinhibition in children and the elderly. They are approved for the treatment of panic disorder (alprazolam, lorazepam), generalized anxiety disorder (alprazolam, clonazepam), insomnia (flurazepam, temazepam), and alcohol withdrawal (chlordiazepoxide, diazepam, oxazepam). Benzodiazepines are also the primary pharmacologic treatment of catatonia and frequently used in combination with antipsychotics to treat agitation.

### Carbamazepine and Related Antiepileptic Drugs

Carbamazepine has been used for over 25 years to treat mania in bipolar disorder; the long-acting formulation is now FDA-approved for the treatment of acute mania (8). It also appears to be effective in the maintenance phase of bipolar disorder in that it prevents recurrent mood episodes (8). Oxcarbazepine has been studied for bipolar

**TABLE 38.3 Anticonvulsants Used in Psychiatry**

MEDICATION	TYPICAL ORAL ADULT DOSE RANGES	PRINCIPLE USES IN PSYCHIATRY	FDA-APPROVED PSYCHIATRIC INDICATIONS
Clonazepam	0.25–1 mg every 12 hours	Panic disorder, anxiety	Panic disorder
Diazepam	2–10 mg every 6–8 hours	Anxiety, alcohol withdrawal	Generalized anxiety, alcohol withdrawal
Lorazepam	0.5–2 mg every 6 hours	Anxiety, agitation, alcohol withdrawal	Generalized anxiety
Carbamazepine	200–600 mg twice daily	Bipolar mania, mixed episodes, bipolar maintenance, impulsivity, aggression, alcohol withdrawal	Bipolar mania or mixed episode
Oxcarbazepine	150–600 mg twice daily	Bipolar mania, mixed episodes, bipolar maintenance, impulsivity, aggression	None
Valproate	15–20 mg/kg in two to three divided doses	Bipolar mania, bipolar maintenance, impulsivity, aggression, alcohol withdrawal	Bipolar mania
Lamotrigine	200 mg/day (up to 400 mg/day in presence of enzyme inducing agent)	Bipolar maintenance, bipolar and refractory depression	Bipolar maintenance
Gabapentin	300–600 mg three times a day	Anxiety, social anxiety disorder	None
Pregabalin	75–150 mg twice daily	Anxiety, generalized anxiety disorder	None (approved for generalized anxiety disorder in Europe)
Tiagabine	4–16 mg two to three times a day	Anxiety, generalized anxiety disorder	None
Topiramate		Alcohol withdrawal and dependence, binge eating, weight loss in antipsychotic-associated weight gain	None

**TABLE 38.4 Adverse Psychotropic Effects of Anticonvulsants**

MEDICATION	PSYCHOTROPIC ADVERSE EFFECTS
Barbiturates	Sedation, cognitive slowing, depression, dependence, withdrawal
Phenytoin	Cognitive slowing, confusion
Benzodiazepines	Sedation, cognitive slowing, anterograde amnesia, dependence, abuse and withdrawal
Carbamazepine	Fatigue, cognitive slowing
Valproate	Somnolence, cognitive slowing
Lamotrigine	Somnolence, fatigue, cognitive slowing
Gabapentin	Somnolence, fatigue
Pregabalin	Somnolence, fatigue
Tiagabine	Somnolence, fatigue, impaired concentration
Topiramate	Somnolence, cognitive slowing, impaired concentration, memory and language; confusion, depression
Levetiracetam	Somnolence, depression, irritability, mood swings

disorder and though it has a better tolerability profile, does not appear to be as effective as carbamazepine in mania or bipolar maintenance treatment in most studies. It may be helpful in reducing aggression and impulsivity, but more research is needed. Carbamazepine has also been used to treat impulsivity and aggression in traumatic brain injury and developmental delay; however, there is inadequate evidence to support this use. Carbamazepine has been shown to be an effective treatment for mild-to-moderate alcohol withdrawal, though it is not widely used as a sole agent for this. Carbamazepine does not appear to cause significant psychotropic side effects, except possibly mild cognitive dulling in some patients.

### Valproate

Valproate is widely used to treat bipolar disorder presenting with mania or mixed manic-depressive features. Valproate also appears to delay recurrent mood episodes and is effective in maintenance treatment of bipolar disorder. Thus, valproate should likely be the first-line agent for patients with comorbid epilepsy and bipolar disorder (8). There is some evidence for valproate's efficacy in treating aggression,

though studies to date have been small. Valproate may be a useful adjunct to benzodiazepines in treating alcohol withdrawal and has been shown to be as effective as phenobarbital and benzodiazepines in treating alcohol withdrawal in other studies.

### Lamotrigine

Lamotrigine has been approved for the treatment of bipolar disorder in the maintenance phase, and appears to specifically prevent the occurrence of depressive, but not manic, episodes. It has no role in treating acute mania or depression, however, and its impact on recurrent depressive episodes appears to be modest. However, it has been shown to be superior to valproate and levetiracetam in improving depressive symptoms among patients with epilepsy and thus might have a role for patients with depressive symptoms or episodes and epilepsy (8). Agitation and aggression due to lamotrigine has been described among patients with epilepsy and developmental delay. The FDA meta-analysis of RCT examining lamotrigine for a variety of conditions including psychiatric, pain, and epilepsy, showed a significant increased risk of suicide compared to placebo across studies (12). Additional psychotropic adverse effects include fatigue, somnolence, and, more rarely, confusion and cognitive slowing.

### Gabapentin

Gabapentin has been used off-label for a variety of disorders in psychiatry. The bulk of the evidence shows that gabapentin is not effective in bipolar disorder, nor in panic or in generalized anxiety disorder. It may have some benefit in social anxiety disorder, but is not approved for this indication. Gabapentin can lead to sedation when used in high dose; abuse, dependence, and withdrawal have also been described.

### Pregabalin

Pregabalin has demonstrated efficacy in treating generalized anxiety disorder in a number of randomized, short-term, placebo-controlled trials with an effect size at least as large as SNRIs (3); it is approved in Europe for this indication. It can be used alone or with antidepressants to treat GAD, and can serve as an augmentation strategy for patients who do not improve adequately on antidepressants alone. Pregabalin is generally well tolerated at typical doses, but may cause somnolence and dizziness.

### Tiagabine

Tiagabine has been shown to be an effective treatment for generalized anxiety disorder, but the magnitude of effect and strength of the evidence is much weaker than that for SSRIs and even pregabalin (3).

### Topiramate

Topiramate does not appear to be effective in bipolar disorder or anxiety disorders. It has been studied in binge eating disorder with significant benefit compared to placebo, and it also promotes weight loss in patients with antipsychotic-associated weight gain. Topiramate also appears to reduce heavy drinking among alcohol-dependent patients and may have a role in treating alcohol craving and withdrawal, but more study is needed. Psychiatric side effects are common with topiramate and include cognitive slowing, confusion, irritability, and depression (8).

### Levetiracetam

Levetiracetam does not appear to have any benefit in psychiatric disorders. Conversely, negative mood effects have been noted with depression, irritability, aggression, and psychosis being reported, particularly among patients with comorbid psychiatric disorders (8). For this reason, levetiracetam should be avoided in patients with a history of mood disorder or psychosis.

## SEIZURE RISK AND PSYCHOTROPICS

Certain psychotropics may increase the risk for seizures, complicating treatment of comorbid psychiatric conditions or leading to the emergence of seizures in vulnerable patients. Factors associated with increased seizure risk among patients taking psychotropics include personal or family history of epilepsy, cerebral atherosclerosis, increased age, general physical illness, and rapid dose escalation.

### Antidepressant Medications

Confounding the literature on antidepressants is the fact that depression and epilepsy tend to co-occur and, thus, any observed increase in seizure risk is likely more related to this association than medication per se. Moreover, depression itself is associated with an increase in rate of seizure compared to the general population, with rates of seizure up to 19 times higher in the placebo arm of trials examining antidepressants for the treatment of depression (13).

Animal models have shown that among the TCAs, imipramine has the most propensity to cause neuronal excitability with increasing drug levels, while amitriptyline shows similar activity but of lesser magnitude. Clomipramine, which is often used in OCD, has a relatively high risk of seizure incidence of 1.34% annually and appears to increase in a dose-dependent fashion. The SSRIs and SNRIs as a group do not appear to be associated with clinically relevant seizure risk except in severe serotonin syndrome due to large overdoses. Citalopram, escitalopram, fluoxetine, and sertraline have all been evaluated in open-label trials among patients with epilepsy and were actually associated with decreased seizures. Moreover, SSRIs have been shown to



have anticonvulsant effects in animal models (13). Trazodone and doxepin, used most typically in low doses to treat insomnia, also appear to confer little seizure risk (14).

Bupropion, which is used to treat depression and to aid smoking cessation, was found to be associated with increased risk of seizures in preapproval studies and risk appears to be dose related. Seizure rate has been reported to be about 1% at daily doses of less than 300 mg, about 2.5% at 300 to 599 mg, and about 4.5% at doses above 599 mg (14). The incidence of seizures seen with sustained-release bupropion is lower; across Phases I–III clinical trials 0.1% patients treated for depression developed seizures (13). Prescribing guidelines suggest that bupropion be avoided in individuals with prior head trauma, epilepsy, and bulimia nervosa.

### Antipsychotic Medications

Antipsychotic medications are associated with some increased risk of seizure, though the magnitude is clinically relevant only for select agents. Clozapine, which is used primarily to treat refractory schizophrenia, induces remarkable EEG changes even at low doses, and such changes are generally correlated with serum drug concentrations. It is the only psychotropic medication to have received an FDA black box warning regarding seizure risk. Clozapine yielded a seizure incidence of 3.5% across phases II–III clinical trials (13) and, in another study, showed cumulative risk of 10% of seizures among patients taking the medication over an almost 4-year period (14). Higher dose, rapid titration, and a diagnosis of seizure disorder are associated with the most risk of seizure in the setting of clozapine, and thus it is to be avoided in patients with epilepsy. Chlorpromazine, which has fallen out of use in psychiatry, is associated with EEG abnormalities, probably due to its sedating effects and appears to confer more seizure risk than nonsedating first-generation antipsychotics such as haloperidol, fluphenazine, pimozide, and trifluoperazine. Chlorpromazine has been associated with seizures in 1% to 2% of patients taking the agent and should be avoided in patients with epilepsy (14).

Nonspecific slowing and epileptiform EEG abnormalities have been observed with olanzapine, which is structurally related to clozapine, and appears to have more seizure risk than the other second-generation antipsychotics such as risperidone, ziprasidone, and aripiprazole (13). Quetiapine appears to be closer to olanzapine in terms of seizure risk. Using data from phases II and III trials, the rank of second-generation antipsychotics with the highest to lowest incidence of seizures is olanzapine, quetiapine, ziprasidone, aripiprazole, and lastly risperidone; with an incidence ranging from 0.9% to 0.3%, respectively (13). Overall, among the antipsychotics, haloperidol and risperidone appear to be the safest with regard to the seizure threshold, but they have higher risk for extrapyramidal symptoms and TD compared to other second-generation antipsychotics. Thus, aripiprazole might be a better option as it also does not appear to confer much risk for seizure and has less motor side effects. A more precise method of estimating seizure risk is the calculation of the seizure incidence ratio (SIR), which takes into account differences in time exposed to the medications due to trial length and allows for more valid comparison across psychotropic agents. The SIRs indicate that once clozapine, olanzapine and quetiapine are excluded, second-generation antipsychotics are not associated with a significantly increased risk of seizure (13) (Table 38.5).

Psychiatric comorbidity is common among patients with epilepsy. The presence of psychiatric symptoms or history should be considered in the choice of AED in order to limit negative psychotropic effects or to potential improve psychiatric symptoms. Seizure risk with psychotropics appears minimal to nonexistent, except for the antidepressants bupropion and clomipramine; and the antipsychotics chlorpromazine, clozapine, olanzapine, and quetiapine. AEDs do not appear to confer a class effect on increased risk for suicidal thoughts or behavior. Some evidence suggests that topiramate, lamotrigine, and

**TABLE 38.5 Psychotropic Medications that Lower the Seizure Threshold**

MEDICATION	SIR [95% CI]	COMMENT
All antidepressants except bupropion immediate release	0.31 [0.21–0.43]	SSRIs are associated with lower seizure incidence relative to placebo
Bupropion immediate release	1.58 [1.03–2.32]	Statistically significant increased seizure incidence with bupropion
All antipsychotics, excluding clozapine, olanzapine, and quetiapine	1.03 [0.77–1.35]	No increase in seizures with antipsychotics other than clozapine, olanzapine, quetiapine
Clozapine	9.5 [7.27–12.20]	Statistically significant increased seizure incidence with clozapine
Olanzapine	2.5 [1.59–3.74]	Statistically significant increased seizure incidence with olanzapine
Quetiapine	2.05 [1.21–3.23]	Statistically significant increased seizure incidence with quetiapine

Abbreviations: SIR, Standardized incidence ratio; [95% CI], 95% confidence interval

Source: Adapted from Ref. (13). Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry*. 2007;62:345–354.

levetiracetam might confer an increased risk for suicidality, but this is not conclusive and may depend on patient population. Overall, increased risk of suicidality may be more related to co-occurring risk factors for suicidality in epilepsy, which require assessment and monitoring among patients with epilepsy.

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# Social Issues

*David M. Labiner*

Living with epilepsy is fraught with difficulties not endured by individuals without epilepsy. Issues include the fact that individuals with epilepsy tend to be less well educated, are under- or unemployed, have lower incomes, and are less likely to be married and have children (1). Much of the stigma associated with epilepsy leads to lower quality of life. Further, other features of epilepsy including discrimination, some of which is legal, lead to practical problems in daily life. Other restrictions placed on individuals with epilepsy, such as limited driving, also may cause poorer quality of life. This chapter will explore some of these issues and how clinicians may assist their patients in addressing these problems.

## STIGMA

Stigma associated with epilepsy has a long history and has been pervasive for centuries. This history is well documented elsewhere (2) but to summarize, epilepsy has been associated with “madness,” demonic possession, criminal behavior, and other undesirable characterizations. Even the description of an individual with epilepsy as an “epileptic” may lead that person to feel stigmatized as they are no longer considered normal. Although the term “epileptic” is still widely used, the phrase “individual with epilepsy” is preferred, in that it does not define the individual as a disease entity.

Stigma is not limited to advanced or developing countries but in fact is observed worldwide. One theory suggests that the stigma arises from a pragmatism regarding the individual with epilepsy as being unable to perform normal societal roles (3,4). However, there are clear differences in the misunderstanding of epilepsy between rich and poor countries that may play a role in the ongoing stigma associated with this disorder (Table 39.1).

The stigma associated with epilepsy may be felt as early as childhood when the diagnosis is first made. Parents may react negatively to the diagnosis, as might teachers, friends, and family, leading the child to be ashamed of the diagnosis. This self-inflicted perception can then be reinforced elsewhere and by others. Studies in different countries have suggested that the public perception of epilepsy, although improving, remains problematic. Individuals with epilepsy

have been viewed as less favorable than those with cerebral palsy or mental illness (5). Studies in the United States and the United Kingdom have shown negative public attitudes toward those with epilepsy. These studies suggest that the public views individuals with epilepsy as potentially violent, antisocial, retarded, or unattractive. In general, negative attitudes have been seen in a diverse group of individuals, including health care providers (6).

One-quarter of individuals with newly diagnosed epilepsy report feeling stigmatized. This number decreases to 10% in individuals who are seizure free 2 years later versus 45% in those who continue to have seizures (6,7). More important, however, is the relationship of stigma with quality of life. It seems intuitive that quality of life is poorer in those who feel stigmatized and this has been borne out in studies (8). These feelings are likely compounded by the negative effects of ongoing seizures as well as medication side effects.

Stigma and its resulting deleterious effect on quality of life is an ongoing problem for the patients. There is no good answer for how best to handle this but local chapters of the Epilepsy Foundation (EF) may have support groups where patient’s or families may get together to discuss common problems and potential solutions. One can locate their local affiliate at [www.epilepsy.com](http://www.epilepsy.com) (click FIND US) (9). It may become necessary to refer a patient for professional counseling or psychiatric care if the stigma and resulting reduction in quality of life lead to a worsening of comorbid depression or for help in developing better coping skills.

## THE AMERICANS WITH DISABILITIES ACT

The Americans with Disabilities Act (ADA) was enacted in 1990 in the United States in an attempt to provide civil rights protections to those with disabilities and as such prohibit discrimination against them. There are five sections within the act that prohibit discrimination on the basis of disability in employment, programs, and services of state and local governments (including education), by places of public accommodation, in public and private transportation services and in communications (Americans with Disabilities

**TABLE 39.1 Etiologies of Epilepsy as Understood by the Public**

RICH COUNTRIES	POOR COUNTRIES
Stress, pressure	Sorcery, witchcraft
Tiredness	Demonic possession, ancestral spirits
Heat	Infection, contagion
Mental illness	Saturation by foams
Brain or nervous disorder	Insect, lizard in stomach or head
Congenital problem	
Old age	

Source: Modified from Ref. (6). Jacoby A, Snape D, Baker GA. Social aspects: epilepsy stigma and quality of life. In: Engel J, Pedley TA. eds. *Epilepsy: a comprehensive textbook*. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008.

Act. 42 U.S.C. 12101 *et seq* 1990). While epilepsy is not specifically mentioned in the ADA, the act clearly modeled from the Rehabilitation Act of 1973 that does include epilepsy.

It is important to recognize that every individual with epilepsy will not be considered to have a disability under the ADA. Epilepsy is considered a disability protected by this statute when, after mitigating measures (such as medication, surgery, and diet) the epilepsy still impacts one or more major life activities (seeing, hearing, walking, working, caring for oneself, sleeping).

Following enactment, court rulings, including those of the Supreme Court, lead to a situation where individuals with disability as defined by the Rehabilitation Act were not protected by the ADA. In 2008, the ADA Amendments Act was passed into law to reinstate the initial intent of the law. The employment portion of this law arguably has had the greatest impact for adults with epilepsy and will be explored further.

Title 1 of the ADA has three primary components. First, it states that no employer with more than 15 employees shall discriminate against a qualified person with a disability because of the disability. The individual must be able to perform the essential function of the job or could do so with reasonable accommodation by the employer. However, employers are not required to do this if it would create an undue hardship on the operation of the employer's business.

The ramification of this law, for individual with epilepsy, is that it helps level the playing field. It is not an affirmative action program. The individual with epilepsy must be able to perform the essential functions of the job with or without reasonable accommodation. As health care providers, we are often asked by patients for guidance when they are seeking employment. It is important to counsel them (or refer them for additional information, see next paragraph) that there is no requirement to self-disclose their condition

(disability) at the time of an application or interview. The employer is forbidden to make disability-related inquiries during the application process. Medical examinations are only allowed after an offer has been made to the individual and drug testing, if required, must be for all persons, not just selected individuals. As treating physicians, we are often asked to opine on what reasonable accommodations should be made for our patients with epilepsy. While these accommodations should be individualized, they could include things such as allowing for a modified work schedule, training of coworkers on seizure first aid, removing flashing lights from the workplace, or having another employee climb a ladder.

While it is impossible for most treating physicians to remember details of laws, the Department of Justice has a website devoted to the ADA, [www.ADA.gov](http://www.ADA.gov) (10).

## EDUCATION

While the majority of children with epilepsy will function relatively normally in school, provisions of the law assure that a child who is disabled (with epilepsy or another disability) is protected. The Individuals with Disabilities Education Act (IDEA) mandates that public schools provide a free, appropriate public education in the least restrictive environment, based on the child's needs ([www.idea.ed.gov](http://www.idea.ed.gov)) (11). Part of this law requires that in Individual Educational Program (IEP) be designed for the child. Physicians may be called upon to assist parents and the schools in developing a plan to deal with the specific individual needs of the child, as the law stipulates that the IEP must be developed by a team of knowledgeable persons and reviewed annually. Physicians also may be called on if the parents disagree with the IEP and wish to appeal through a due process hearing and review.

## SOCIAL SECURITY

In the United States, Social Security is available for individuals with a severe impairment, resulting in an inability to work that is likely to last for greater than 12 months. Epilepsy is a listed impairment in the Social Security guidelines (12). The rules are written such that there are distinctions between convulsive and nonconvulsive seizures. One would be considered eligible for benefits if they have a documented typical seizure pattern whereby the seizures occur more frequently than once per month despite 3 months of prescribed medical treatment. These episodes typically are diurnal but may be nocturnal if they significantly interfere with daytime activities. Nonconvulsive seizures need to occur more frequently than once per week and should be associated with an alteration of awareness, loss of consciousness, or postictal behavioral abnormalities that interfere with normal functioning. Patients should be made aware that the determination of disability for the purpose of Social Security is initiated by the individual themselves



by contacting their local Social Security offices and requesting assessment. The role of the treating physician is to provide to the Social Security Administration medical records and timely reports regarding the patient's seizures, when requested.

### MEDICAL INSURANCE

Obtaining medical insurance, while a nonissue in many places around the world, has been a significant problem for individuals with epilepsy in the United States. This has been caused by the restrictive "preexisting disease" clauses present in many policies. With the passage of the Affordable Healthcare Act, this provision is being phased out and will allow individuals with epilepsy to obtain insurance that includes coverage for their epilepsy.

### DRIVING

One of the most problematic restrictions placed on individuals with epilepsy is the restriction regarding driving. While laws differ all over the world, and in each of the 50 United States, model legislation has been proposed to account for the public safety and an individual's need for transport (13). Most authorities in the field agree that individuals with epilepsy should be allowed to drive following some specified seizure-free interval (typically 3 to 24 months). The trend over the past few decades has been toward shortening this interval. The EF has an on-line database where one can check the laws in their specific state (14). A summary of these restrictions can be seen in Table 39.2. Physicians must know the laws for their state (and possibly neighboring states), particularly if there is mandatory reporting of an individual to the motor vehicle agency of that state. Only six states still require mandatory reporting by the physician: California, Delaware, Nevada, New Jersey, Oregon, and Pennsylvania. Physicians are provided immunity for reporting in states where it is required and more typically, "good faith" immunity if they choose to report in a state where it is not required, provided they believe the patient is a threat to public safety because they are driving against medical advice. More typical, however, is the admonition that the physician discuss the laws of the local jurisdiction with the patient and that the patient understand the laws. This of course should be appropriately documented in the patient's medical record. Physicians have been found liable when their patients with epilepsy have injured others, if they have not informed them of the appropriate laws. In addition, patients themselves have been found liable (either in civil or in criminal cases) when driving against medical advice.

There are a large number of people who believe that individuals with epilepsy should not be allowed to operate a motor vehicle. They typically cite safety concerns and advocate for longer seizure-free periods before allowing unrestricted driving. A study done in Arizona after the

**TABLE 39.2 Driving Restrictions in the United States**

STATE	SEIZURE-FREE PERIOD	MANDATORY REPORTING
Alabama	6 months, with exceptions	No
Alaska	6 months	No
Arizona	3 months, with exceptions	No
Arkansas	1 year with medical evaluation	No
California	3 or 6 months, with exceptions	Yes
Colorado	No defined period	No
Connecticut	No defined period	No
Delaware	No defined period	Yes
District of Columbia	1 year	No
Florida	2 years or 6 months if under M.D. care	No
Georgia	6 months	No
Hawaii	6 months, with exceptions	No
Idaho	No defined period	No
Illinois	No defined period	No
Indiana	No defined period	No
Iowa	6 months with MD report	No
Kansas	6 months, with exceptions	No
Kentucky	3 months	No
Louisiana	No defined period, based on MD recommendation	No
Maine	3 months or 2 years based on prognosis	No
Maryland	3 months, with exceptions	No
Massachusetts	6 months, with exceptions	No
Michigan	6 months, with exceptions	No
Minnesota	3 months with MD recommendation	No
Mississippi	1 year	No
Missouri	6 months with MD recommendation	No
Montana	No defined period, based on MD recommendation	No
Nebraska	No defined period	No
Nevada	3 months, with exceptions	Yes
New Hampshire	1 year, less at DMV discretion	No
New Jersey	1 years, less at DMV discretion	Yes
New Mexico	6 months	No
New York	1 year, with exceptions	No
North Carolina	No defined period, based on MD recommendation	No

(continued)

**TABLE 39.2 Driving Restrictions in the United States (continued)**

STATE	SEIZURE-FREE PERIOD	MANDATORY REPORTING
North Dakota	6 months, restricted license available at 3 months	No
Ohio	No defined period	No
Oklahoma	6 months, with exceptions	No
Oregon	3 months	Yes
Pennsylvania	6 months, with exception	Yes
Rhode Island	18 months, less at DMV discretion	No
South Carolina	6 months	No
South Dakota	6–12 months, less with MD recommendation	No
Tennessee	6–12 months with MD and DMV recommendation	No
Texas	6 months, with exceptions	No
Utah	3 months, with exceptions	No
Vermont	No defined period	No
Virginia	6 months, with exceptions	No
Washington	6 months, with exceptions	No
West Virginia	1 year, with exceptions	No
Wisconsin	3 months, with MD recommendation	No
Wyoming	3 months, with exceptions	No

Source: From Ref. (13). American Academy of Neurology, American Epilepsy Society, and Epilepsy Foundation of America. Consensus statements, sample statutory provisions, and model regulations regarding driver licensing and epilepsy. *Epilepsia*. 1994;35:696–705.

state shortened the seizure-free interval following a last seizure from 12 to 3 months, suggests that there may be no benefit of a longer seizure-free interval (15). Specifically, the authors reported no meaningful difference in accident rates for the 3 years before and after the law changed, after adjusting for changes in population and miles driven. This suggests that the onerous law, still present in some states,

could potentially be adjusted to the benefit of the individual with epilepsy.

Stigma is a difficult and ongoing problem for individuals with epilepsy. It leads to worsened quality of life for patients. Other restrictions, such as driving, negotiating employment accommodations, or dealing with the Social Security system, make life difficult for patients. It is therefore incumbent upon providers to be familiar with the rules that are imposed on patients and serve as their advocates. Further, as health professionals must continue to strive to help remove stigma associated with epilepsy through educational efforts to the patients themselves, their families, and the general public.

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# Metabolic Epilepsies

*Abeer J. Hani and Mohamad A. Mikati*

The spectrum of metabolic conditions causing epilepsy continues to expand, allowing for further identification of the etiologies of various epilepsies. Keeping track of these disorders can prove to be a daunting task for clinicians. A useful online resource in this regard is [www.orpha.net](http://www.orpha.net) that keeps a frequently updated database of the clinical manifestations of rare diseases, how to diagnose them, and of their potential treatments. In this chapter, a framework will be presented that permits clinicians to identify a patient with a possible metabolic epilepsy, assess the associated clinical features and neurophysiologic findings, and develop a diagnostic approach to such epilepsies. A brief overview of some of the more common metabolic epilepsies will be provided. For more details about the various inherited metabolic epilepsies, the reader is referred to more comprehensive reviews (1).

## ETIOLOGIES

In many of the metabolic epilepsies that will be discussed in the further sections, occasional triggered seizures may occur in the setting of hypoglycemia or hyperammonemia. However, there is an intrinsic underlying epilepsy component in these conditions. It is thought that the pathogenesis of these conditions could be related to energy deficiency, toxic effects, impaired neuronal function, disturbance of neurotransmitter systems, associated brain malformations, vitamin or cofactor dependency, or vitamin transporter defects (Table 40.1) (2).

## CLINICAL FEATURES

While such epilepsies often have unique clinical presentations, the following features may suggest a possible metabolic epilepsy. Onset is usually in the neonatal, infantile, or early childhood periods and rarely in adulthood (Table 40.2)(2,3). In the neonatal period, there may be reports of hypotonia, poor feeding, lethargy, respiratory distress, or lactic acidosis in combination with myoclonic seizures. In addition to myoclonic seizures, certain seizure types and

**TABLE 40.1 Pathogenesis of Common Metabolic Epilepsies**

PATHOGENESIS	METABOLIC EPILEPSY
Energy deficiency	Glucose transporter -1 (GLUT1) deficiency Respiratory chain deficiency Pyruvate dehydrogenase deficiency Krebs cycle defects Creatine deficiencies
Toxic effects	Aminoacidopathies Organic acidurias Urea cycle defects Molybdenum cofactor deficiency Sulfite oxidase deficiency
Impaired neuronal function	Storage diseases
Disturbance of neurotransmitter system	Nonketotic hyperglycinemia Atypical phenylketonuria GABA transaminase deficiency Succinic semi-aldehyde dehydrogenase deficiency
Associated brain malformations	Peroxisomal disorders (Zellweger syndrome) Respiratory chain deficiency Pyruvate dehydrogenase deficiency O-glycosylation defects (congenital muscular dystrophies)
Vitamin or cofactor dependency and vitamin transporter defects	Biotinidase deficiency Pyridoxine-dependent and pyridoxal 5'-phosphate-dependent epilepsy (folinic-acid-responsive seizures) Thiamine transporter deficiency Menkes' disease Folate transporter defect (FOLR1) Dihydrofolate reductase deficiency
Miscellaneous	Serine biosynthesis deficiency

Source: Modified from Ref. (2). Dulac O, Plecko B, Gataullina S, Wolf NI. Occasional seizures, epilepsy, and inborn errors of metabolism. *Lancet Neurol.* 2014;13:727–739.

**TABLE 40.2 Metabolic Epilepsies Stratified by Age at Manifestation**

AGE AT MANIFESTATION	METABOLIC EPILEPSY
Neonatal	<ul style="list-style-type: none"> <li>– Pyridoxine-dependent epilepsy (including folinic-acid-responsive seizures)</li> <li>– Pyridox(am)ine 5-phosphate deficiency</li> <li>– Nonketotic hyperglycinemia</li> <li>– Urea cycle defects</li> <li>– Holocarboxylase synthase deficiency</li> <li>– Molybdenum cofactor deficiency</li> <li>– Sulfite oxidase deficiency</li> <li>– Organic acidurias</li> <li>– Zellweger syndrome</li> <li>– Neonatal adrenoleukodystrophy</li> <li>– Adenylosuccinate lyase deficiency</li> <li>– Dihydrofolate reductase deficiency</li> </ul>
Infancy	<ul style="list-style-type: none"> <li>– Glucose transporter-1 (GLUT1) deficiency</li> <li>– Creatine deficiency</li> <li>– Biotinidase deficiency</li> <li>– Aminoacidopathies</li> <li>– Organic acidurias</li> <li>– Congenital disorders of glycosylation</li> <li>– Pyridoxine-dependent epilepsy</li> <li>– Infantile neuronal ceroid lipofuscinosis (CLN1)</li> <li>– Folate and thiamine transporter deficiencies</li> <li>– Peroxisomal disorders</li> <li>– Menkes disease</li> </ul>
Toddlers	<ul style="list-style-type: none"> <li>– Late infantile neuronal ceroid lipofuscinosis (CLN2)</li> <li>– Mitochondrial disorders including Alpers disease</li> <li>– Lysosomal storage disorders</li> <li>– Thiamine transporter deficiency</li> <li>– Folate transporter deficiency</li> </ul>
School age and adolescence	<ul style="list-style-type: none"> <li>– Mitochondrial disorders</li> <li>– Juvenile form of neuronal ceroid lipofuscinosis (CLN3)</li> <li>– Progressive myoclonic encephalopathies</li> <li>– Lysosomal storage disorders</li> <li>– Thiamine transporter deficiency</li> <li>– Lafora disease</li> <li>– Gaucher disease</li> <li>– Niemann-Pick type C disease</li> </ul>
Adulthood	<ul style="list-style-type: none"> <li>– Kufs disease</li> <li>– Juvenile form of neuronal ceroid lipofuscinosis (CLN3)</li> <li>– Sialidosis type 1</li> <li>– Gaucher disease</li> <li>– Mitochondrial diseases (MERRF, MELAS, NARP)</li> <li>– Nonsyndromic respiratory chain disorders</li> <li>– Lafora disease</li> <li>– Acute porphyrias</li> <li>– Wilson disease</li> <li>– GLUT1 deficiency</li> <li>– Creatine metabolism defects</li> <li>– SSADH deficiency</li> <li>– Urea cycle defects</li> <li>– Cerebrotendinous xanthomatosis</li> <li>– Metachromatic leukodystrophy</li> <li>– Adrenoleukodystrophy</li> </ul>

Source: Modified from Refs. (2) and (3).

Abbreviations: MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke; MERRF: myoclonic epilepsy with ragged red fibers; NARP: neuropathy, ataxia, and retinitis pigmentosa; SSADH: succinic semialdehyde dehydrogenase.



**TABLE 40.3 Classification of Some Metabolic Epilepsies According to the Presenting Seizure Type or Epilepsy Syndrome**

SEIZURE TYPE/ EPILEPSY SYNDROME	METABOLIC EPILEPSY
Infantile spasms	<ul style="list-style-type: none"> <li>– Biotinidase deficiency</li> <li>– Menkes disease</li> <li>– Mitochondrial disorders</li> <li>– Organic acidurias</li> <li>– Amino acidopathies</li> </ul>
Myoclonic seizures	<ul style="list-style-type: none"> <li>– Nonketotic hyperglycinemia</li> <li>– Mitochondrial disorders</li> <li>– GLUT1 deficiency</li> <li>– Storage disorders</li> </ul>
Atypical absence	<ul style="list-style-type: none"> <li>– GLUT1 deficiency</li> </ul>
Progressive myoclonic epilepsies	<ul style="list-style-type: none"> <li>– Lafora disease</li> <li>– Mitochondrial diseases (MERRF, MELAS)</li> <li>– Unverricht–Lundborg disease</li> <li>– Sialidosis</li> </ul>
Epilepsy with generalized tonic–clonic seizures	<ul style="list-style-type: none"> <li>– GLUT1 deficiency</li> <li>– Neuronal ceroid lipofuscinosis (NCL2/ NCL3)</li> <li>– Other storage disorders</li> <li>– Mitochondrial disorders</li> </ul>
Epilepsia partialis continua	<ul style="list-style-type: none"> <li>– Mitochondrial disorders with mutations in DNA polymerase gamma (Alpers disease).</li> </ul>
Status epilepticus	<ul style="list-style-type: none"> <li>– Pyridoxine-dependent epilepsy</li> <li>– Alpers syndrome</li> </ul>

Source: Modified from Ref. (4). Bahi-Buisson N, Dulac O. Epilepsy in inborn errors of metabolism. *Handb Clin Neurol*. 2013;111:533–541.

epilepsy syndromes may be associated with specific metabolic epilepsies (Table 40.3) (4). Family history of similar presentations warrants further genetic and metabolic investigations. Refractoriness of the seizures to traditional antiepileptic drugs (AEDs) often raises a red flag in the neonatal and infantile age group for a possible metabolic etiology. A detailed history ought to be obtained to exclude other potential etiologies, including prenatal or perinatal events, head trauma, infections, or other systemic diseases. Physical examination should be detailed, focusing on features that can suggest other etiologies as well as those that could suggest metabolic etiologies. One should look for the presence of dysmorphic features or neurocutaneous stigmata, head size abnormalities, and various manifestations of systemic involvement. In addition to the seizures, other neurologic manifestations may be present and may predate or follow the seizures. These may include developmental delay/regression, intellectual disability, movement disorders, micro- or macrocephaly, and other cerebral gray or white matter changes.

### ELECTROENCEPHALOGRAPHY

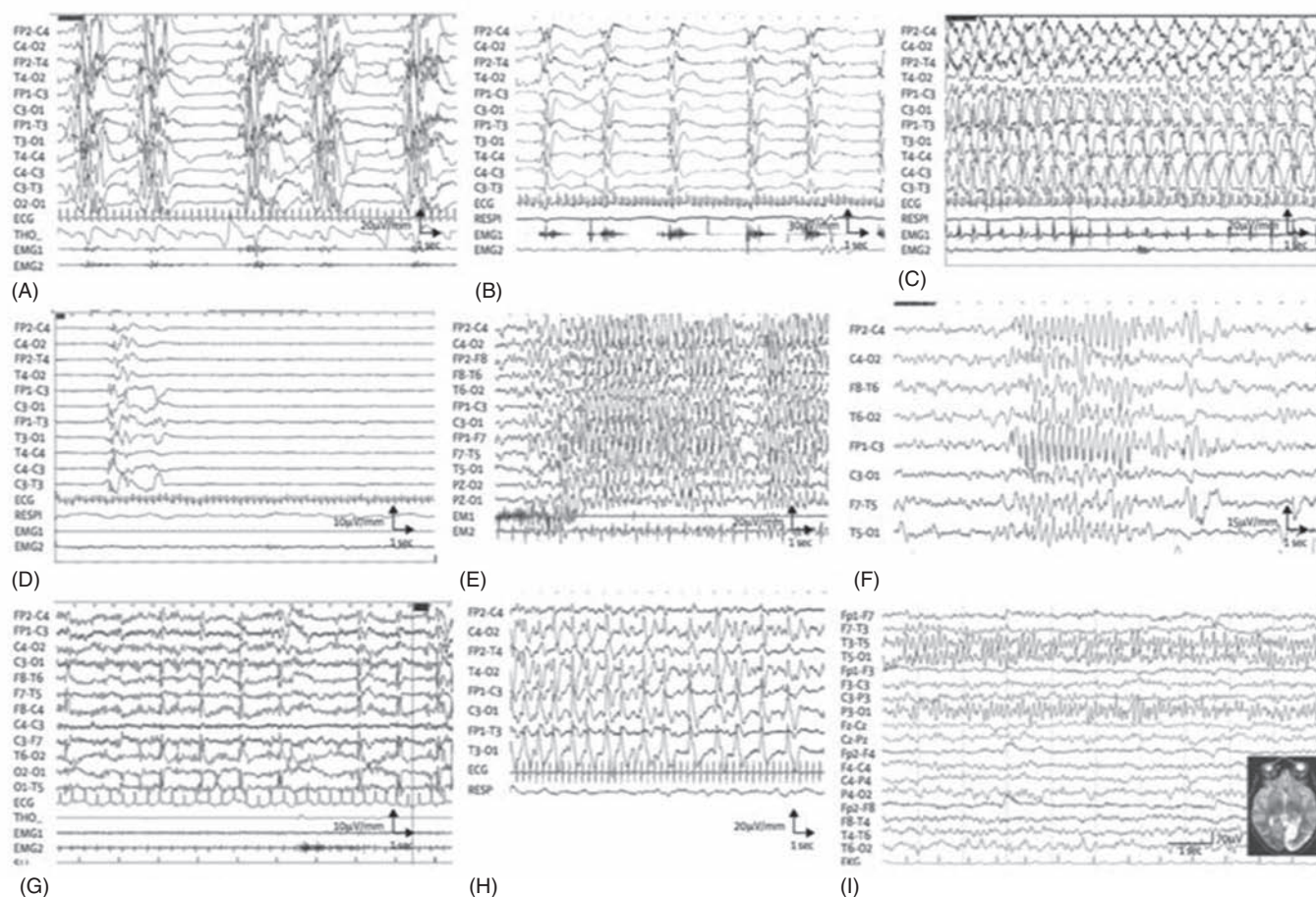
Given that multiple seizure types or epilepsy syndromes may be the presenting manifestations of metabolic epilepsies, an array of EEG presentations similarly exists (Figure 40.1). Although there are no pathognomonic EEG signatures of metabolic diseases, certain patterns may be associated with specific metabolic epilepsies (Table 40.4)(1).

In general, early-onset myoclonic metabolic epilepsy often manifests with burst suppression and/or irregular polyspike wave paroxysm during myoclonus. At times, hypersarrhythmia may be seen and rarely more specific patterns, such as the comb-like rhythm in maple syrup urine disease, may suggest a diagnosis. In progressive metabolic epilepsies, serial EEGs show progression from normal background to slowing, loss of sleep architecture, and an increased burden of generalized spike-and-wave activity.

### NEUROIMAGING

Often the key features in the neuroimaging of this group of epilepsies include brain atrophy with symmetric findings. There may be myelination abnormalities with infrequent contrast enhancement (5). In certain metabolic epilepsies, there may be evidence of brain malformations, such as corpus callosal agenesis in glycine encephalopathy and pyruvate dehydrogenase deficiency or polymicrogyria in Zellweger syndrome. At times, predominant anatomic location of the white matter changes may suggest the diagnosis. White matter abnormalities are more anterior in Alexander disease, posterior in adrenoleukodystrophy, central in metachromatic leukodystrophy, diffuse in Pelizaeus-Merzbacher disease, and peripheral in L2-OH-glutaric aciduria (Figure 40.2).

It is useful to obtain neuroimaging for patients with metabolic epilepsies early in the course of their disease given that in later stages the findings are similar and consist of diffuse atrophy, reduced white matter volume, and shrunken



**FIGURE 40.1** EEG in selected metabolic epilepsies. (A) Interictal EEG in a 15-day-old baby with nonketotic hyperglycinaemia, showing the characteristic suppression-bursts sequence (bursts of high-amplitude diffuse polyspikes separated by episodes of flat tracing). (B–D) EEG from a 3-month-old baby with pyridoxine-dependent epilepsy. (B) Epileptic spasms in clusters with high-amplitude slow complex and rhythmic waves. (C) High-amplitude rhythmic spike-waves predominate on the left hemisphere during a right clonic seizure. (D) After pyridoxine intravenous injection (100 mg), EEG shows flattening of the tracing. (E) Myoclonic status epilepticus in a 6-year-old girl with guanidinoacetate methyltransferase deficiency. Diffuse high-voltage spikes and spike-waves predominating on frontal or frontal-central areas; myoclonic jerks recorded on deltoid electromyography. (F) Atypical absence in an 11-year-old girl with glucose transporter-1 deficiency, with diffuse high-amplitude spike-waves. (G) Diffuse spikes, predominating on occipital areas triggered by slow photic stimulation in a 5-year-old girl with late-infantile neuronal ceroid lipofuscinosis. (H) A 3-year-old girl with Alpers disease due to *POLG1* mutations. Interictal EEG shows bilateral high-amplitude periodic sharp waves and spike-waves with left occipital predominance. (I) A 16-year-old girl with MELAS and the classic mitochondrial 3243A→G mutation. EEG shows spike and spike-waves rhythmic discharges over the left posterior region, corresponding to the occipital area of hyperintense T2 signal. MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

Source: Adapted from Ref. (2). Dulac O, Plecko B, Gataullina S, Wolf NI. Occasional seizures, epilepsy, and inborn errors of metabolism. *Lancet Neurol.* 2014;13:727–739.

basal ganglia (6). Often, the white matter is predominantly involved with or without involvement of the basal ganglia and thalami. The use of proton magnetic resonance spectroscopy (MRS) may assist in the diagnosis by demonstrating the presence of metabolites that are not normally detected, such as galactitol in galactosemia. Alternatively, MRS may show increased concentrations of metabolites as in Canavan disease or decreased concentrations as in creatine deficiency. Key radiologic features of some metabolic epilepsies are listed in Table 40.5 (7).

## COMMON METABOLIC EPILEPSIES

The spectrum of metabolic epilepsies is expanding. In this section, some of the more common and potentially treatable metabolic epilepsies will be detailed.

### Vitamin B6-Dependent Epilepsies

Vitamin B6-dependent epilepsies are so named because vitamin B6 dependency is caused by a genetically inherited

TABLE 40.4 EEG Patterns of Certain Metabolic Epilepsies

EEG PATTERN	METABOLIC EPILEPSY
Comb-like rhythm	– Maple syrup urine disease – Propionic acidemia
Fast central spikes	– Tay–Sachs disease – Biotinidase deficiency
Rhythmic vertex-positive spikes	– Sialidosis (type I)
Vanishing electroencephalogram	– Infantile NCL (early infantile/ type I/ Haltia-Santavouri)
High-amplitude (16–24 Hz) activity	– Infantile neuroaxonal dystrophy
Giant SSEPs	– Progressive myoclonic epilepsy
Marked photosensitivity	– Progressive myoclonic epilepsy (Lafora) – NCL, particularly late infantile (type II/ Bielschowsky, CLN2)
Burst suppression	– Adrenoleukodystrophy (neonatal) – Citrullinemia – D-glyceric acidemia – Holocarboxylase synthetase deficiency – Vitamin B6-dependent epilepsy – Leigh disease – Mb cofactor deficiency – Menkes syndrome – MTHFR deficiency – NKH – PDH/PC deficiency – Propionic acidemia – Sulfite oxidase deficiency
Hypsarrhythmia	– Adrenoleukodystrophy (neonatal) – CDG (type III) – HHH – Menkes disease – Neuroaxonal dystrophy – Nonketotic hyperglycinemia – Pyruvate dehydrogenase deficiency – Progressive encephalopathy with edema and hypsarrhythmia – Phenylketonuria – Zellweger syndrome
Low-amplitude slowing	– Urea cycle defects (carbamylphosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase)

Source: Adapted from Ref. (1). Pearl PL. *Inherited Metabolic Epilepsies*. New York, NY: Demos Medical, 2012.

metabolic disorder requiring a lifelong need for pharmacologic doses of vitamin B6 and recurrence of seizures upon withdrawal (8). This is in contradistinction to vitamin B6 nutritional deficiency due to severe chronic malnutrition or vitamin B6 responsiveness seen in some epilepsy syndromes due to enhancement of the pyridoxine cofactor function without seizure recurrence upon withdrawal. Vitamin B6 is absorbed in three different vitamers (pyridoxal phosphate, pyridoxine, and pyridoxamine) and is then converted into pyridoxal-5'-phosphate (PLP) that acts as a cofactor in over 100 enzymatic reactions in amino acids and neurotransmitter metabolism.

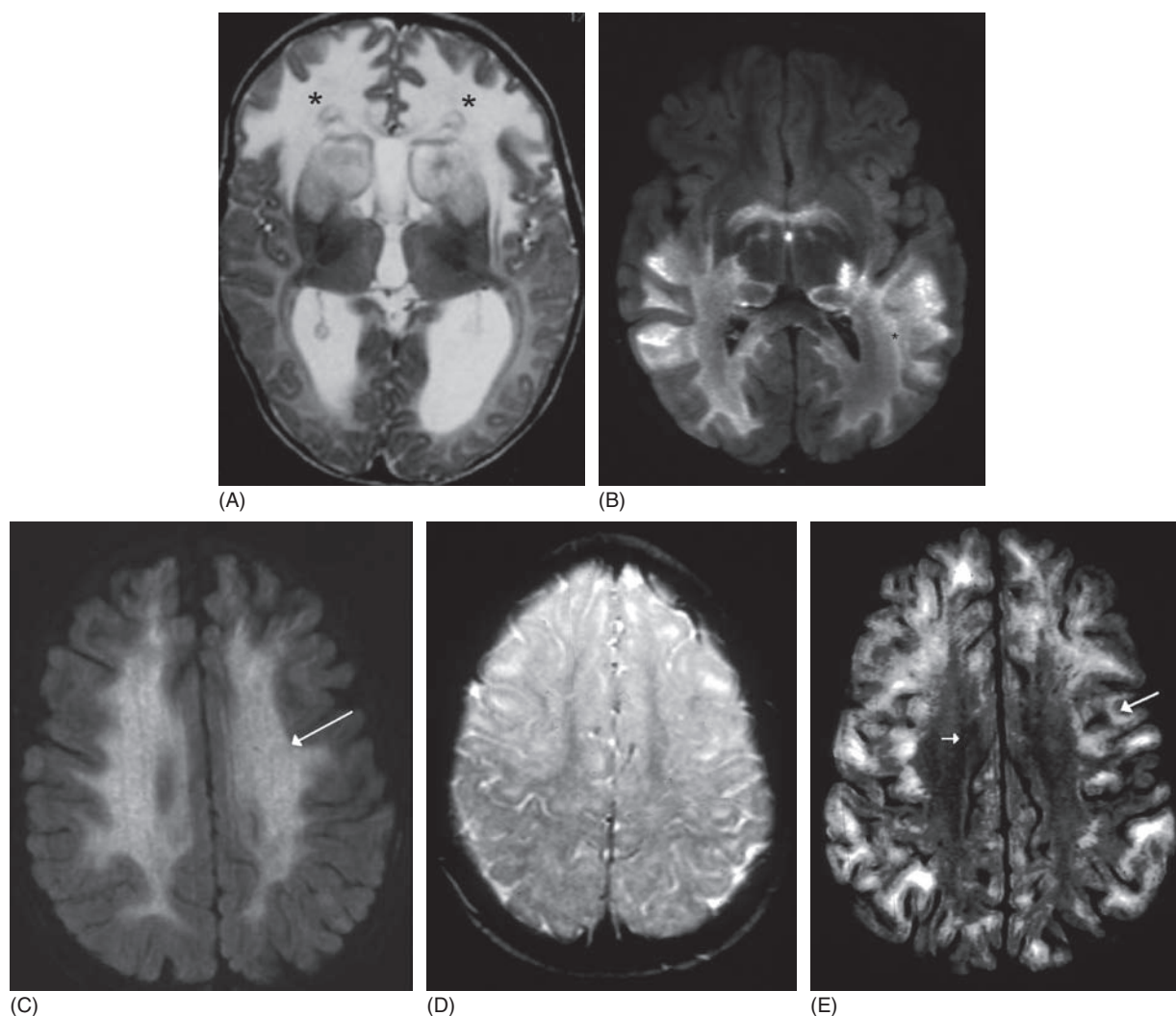
Four inborn errors of metabolism may cause vitamin B6-dependent epilepsies, two are caused by inactivation of PLP resulting in pyridoxine-dependent epilepsy (PDE) and hyperprolinemia type II. The other two are caused

by reduced synthesis and availability of PLP, resulting in PLP-dependent epilepsy and congenital hypophosphatasia.

### *Pyridoxine-Dependent Epilepsy*

PDE is an autosomal recessive epilepsy in which patients present with pharmacoresistant seizures commonly in the neonatal period (and even intrauterine convulsions) and up to 3 years of age. Seizures can be in the form of infantile spasms, partial, myoclonic, or atonic seizures. The EEG initially may be normal or show generalized bursts of high-voltage delta activity interspersed with spike and sharp waves and periods of asynchronous attenuation. Often, treatment with 100 to 300 mg of pyridoxine will stop the refractory seizures or status epilepticus and convert the EEG into burst suppression and later normalization within





**FIGURE 40.2** Differential patterns of white matter involvement on T2 and FLAIR imaging. (A) Frontal white matter involvement in Alexander disease on axial T2 (\*s). (B) Posterior white matter involvement in adrenoleukodystrophy on axial FLAIR (\*). (C) Diffuse central white matter involvement (arrow) with spared subcortical u-fibers in metachromatic leukodystrophy. (D) Diffuse white matter involvement and hypomyelination involving subcortical u-fibers in Pelizaeus-Merzbacher disease. (E) Axial T2 with peripheral white matter hyperintensity (large arrow) sparing central white matter in L2-hydroxyglutaric aciduria (small arrow).

Source: Adapted from Ref. (1). Pearl PL. *Inherited Metabolic Epilepsies*. New York, NY: Demos Medical, 2012.

minutes. While the diagnosis is often initially suggested by the prompt response to pyridoxine, biochemical markers and genetic testing can be used to subsequently confirm the diagnosis. The pathway responsible for PDE is illustrated in Figure 40.3. It is now known that the disease is due to antiquitin deficiency, leading to low levels of cerebral PLP, the active form of vitamin B<sub>6</sub>, and thus impaired cofactor function. Using this pathway, it is now established that elevated pipelicolic acid, alpha-aminoadipic acid semialdehyde (AASA), and L-D1-piperidine 6-carboxylate (P6C) tested in the urine, plasma, or cerebrospinal fluid (CSF) serve as biochemical markers for PDE. Genetically, mutations in the antiquitin gene (*ALDH7A1*) can be determined and may be used to assist with prenatal counseling. Once the diagnosis has been established and confirmed, a treatment trial with 30

mg/kg/day of vitamin B<sub>6</sub> is recommended for 1 to 3 days to help identify responders. The daily maintenance between 50 and 200 mg/day has been suggested. More recently, folinic acid-responsive epilepsies were found to be genetically identical to PDE. Folinic acid may be used as an add-on therapy in case of partial responsiveness to vitamin B<sub>6</sub> or breakthrough seizures at a dose of 3 to 5 mg/kg/day for neonates and a maximum dose of 20 mg in older children. In addition, lysine-restrictive diets are also thought to help with seizure control in patients with PDE.

#### *Pyridoxal-5'-Phosphate-Dependent Epilepsy*

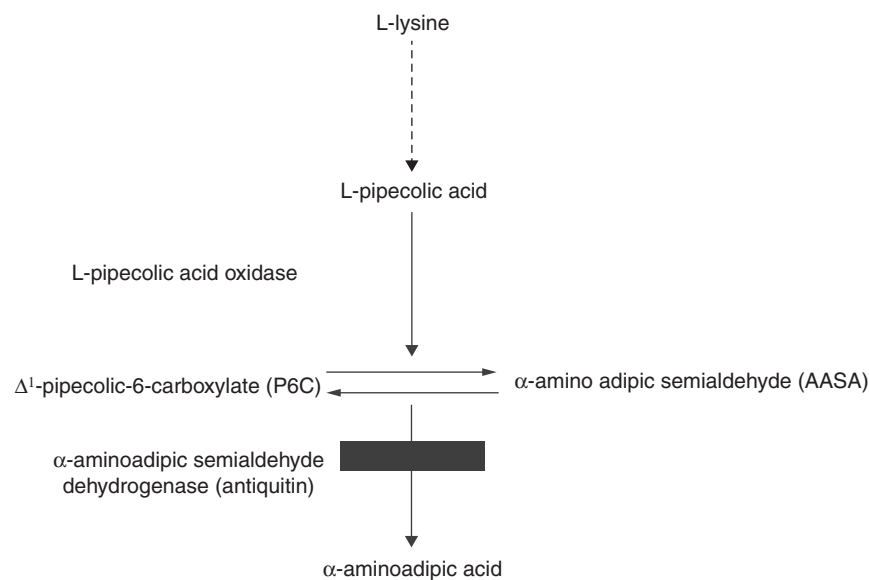
The clinical presentation of pyridoxal-5'-phosphate-dependent epilepsy is similar to that of PDE, but seizures



TABLE 40.5 Key Imaging Features in Some Metabolic Epilepsies

METABOLIC EPILEPSY CATEGORY	SPECIFIC METABOLIC EPILEPSY	KEY POINTS AND IMAGING FEATURES
Urea cycle defects	Urea cycle disorders	Extensive cortical and subcortical abnormalities; thalami sparing
Organic aciduria	Glutaric aciduria	Frontotemporal atrophy, widening of sylvian fissures, and basal ganglia abnormalities
	Maple syrup urine disease	Maple syrup urine disease edema (cytotoxic edema of myelinated white matter) and vasogenic edema of unmyelinated white matter
	Methylmalonic acidemia	Abnormalities of the cerebral white matter and bilateral globus pallidus
	Propionic acidemia	Abnormalities of the cerebral white matter and the corpus striatum
Mitochondrial diseases	Leigh disease (subacute necrotizing encephalopathy)	Symmetric abnormalities of the basal ganglia
	MELAS	Nonterritorial cortical and basal ganglia infarcts
Peroxisomal diseases	Zellweger syndrome	Diffuse white matter abnormality, cortical migration anomalies, and germinolytic cysts
	Refsum disease and neonatal adrenoleukodystrophy	Similar features as in Zellweger syndrome with less severe cortical malformation
	X-linked adrenoleukodystrophy	Symmetric peritrigonal abnormality with involvement of the splenium of the corpus callosum; abnormal peripheral enhancement
Lysosomal diseases	Globoid cell leukodystrophy (Krabbe disease)	Symmetric deep white matter abnormality with dark thalami
	Metachromatic leukodystrophy	Symmetric deep white matter abnormality, with sparing of subcortical u-fibers
	Mucopolysaccharidosis	Symmetric deep white matter abnormality with dilated Virchow-Robin spaces

Source: Adapted from Ref. (7). Ibrahim M, Parmar HA, Hoeffling N, Srinivasan A. Inborn errors of metabolism: combining clinical and radiologic clues to solve the mystery. *AJR Am J Roentgenol*. 2014;203:W315–W327.



**FIGURE 40.3** Enzyme defects and biomarkers in pyridoxine-dependent epilepsy: The accumulating compound alpha-amino adipic semialdehyde (AASA) is in equilibrium with L-D<sup>1</sup>-piperidine 6-carboxylate (P6C). This P6C compound inactivates pyridoxal-phosphate (PLP), leading to severe cerebral PLP deficiency and disturbed cofactor function within amino acid and neurotransmitter metabolism.

Source: Adapted from Ref. (1). Pearl PL. *Inherited Metabolic Epilepsies*. New York, NY: Demos Medical, 2012.

are resistant to pyridoxine but respond to PLP. This epilepsy is also autosomal recessive and is due to a mutation in the pyridox(am)ine 5'-phosphate oxidase (*PNPO*) gene. *PNPO* is needed to convert pyridoxine to its only active cofactor, PLP. Often patients have higher mortality if untreated. Diagnosis is established by low PLP levels in the CSF as well as by genetic testing for *PNPO* gene mutations. PLP is recommended in a dose of 10 to 100 mg/kg/day divided in four to six doses, with the dose titrated to normalize biochemical markers.

### Inborn Errors of Biotin Metabolism

There are two autosomal recessive disorders of biotin metabolism: biotinidase deficiency and holocarboxylase synthetase deficiency. Both disorders lead to deficiency of biotin-dependent carboxylases that often manifest with metabolic acidosis associated with neurological abnormalities and skin disease (skin rashes and/or alopecia) (9).

#### *Biotinidase Deficiency*

Biotinidase deficiency tends to have an insidious and variable presentation. Neurological manifestations include lethargy, hypotonia, seizures, ataxia, developmental delay, hearing loss, visual problems including optic atrophy, and rarely spastic paraparesis. The diagnosis is confirmed by measuring serum biotinidase activity, and mutation analysis of the biotinidase gene is often not needed. Neonatal screening for biotinidase in many countries using whole blood spotted on a filter paper helps in the early identification of the disorder. This allows for prompt treatment with pharmacological doses of biotin (5–20 mg), thus preventing irreversible brain damage caused by late diagnosis and treatment.

#### *Holocarboxylase Synthetase Deficiency*

Holocarboxylase synthetase deficiency presents in a manner similar to biotinidase deficiency but earlier, in the neonatal period or early infancy. Patients may have generalized tonic seizures, partial motor seizures, and multifocal myoclonic jerks. Diagnosis may be established by urine organic acid, enzyme assay, or DNA mutation analysis. Treatment usually consists of 10 to 20 mg/day of biotin, but some patients may require doses as high as 40 to 200 mg/day.

### Disorders of Folate Metabolism

There are multiple disorders of folate metabolism (9) with two that are relevant to the discussion of metabolic epilepsies: cerebral folate deficiency and methyltetrahydrofolate reductase (MTHFR) deficiency.

#### *Cerebral Folate Deficiency*

In cerebral folate deficiency, the level of folate is normal in the plasma and red blood cells, but the level of methyltetrahydrofolate (MTHF) in the CSF is low, which is thought to

be due to decreased transport across the blood–brain barrier. Primary cerebral folate deficiency is thought to be due to lactose-mediated autoantibodies to the cerebral folate receptor or due to impaired transfer of folate to the central nervous system (CNS) caused by loss-of-function mutations in folate receptor 1 (*FOLR1*) gene. Secondary cerebral folate deficiency may be seen in other patients with Rett's syndrome, autistic spectrum, and mitochondrial diseases. Clinical presentation of the primary form typically occurs at 4 to 6 months of age with a picture of slowly progressive encephalopathy, insomnia, deceleration of head growth, hypotonia, delays, spasticity, and epilepsy in one-third of the cases. Diagnosis is established by detection of low MTHF in the CSF. Treatment with folinic acid 0.5 to 5 mg/kg/day helps improve the clinical symptoms and correct the MTHF levels in the CSF.

#### *Methyltetrahydrofolate Reductase Deficiency*

MTHFR deficiency is the most common inborn error of folate metabolism. It results in low levels of 5-MTHF needed to remethylate homocysteine to methionine. Often, there is onset of a slowly progressive encephalopathy in infancy, and children often have microcephaly and intractable seizures. This is different from the late-onset form where seizures are less common and patients present with progressive motor deterioration, recurrent strokes, and psychiatric symptoms. Diagnosis is established by measuring the MTHFR activity in leukocytes, lymphocytes, or cultured fibroblasts, or with mutation analysis. Although the prognosis is overall poor, treatment with betaine, folate, MTHF, and methionine may help stop the seizures.

### Inborn Errors of Creatine Metabolism

Creatine acts as a spatial and temporal buffer in intracellular energy metabolism, taking ATP at its production site and delivering it at its consumption site, thus creatine metabolism is most essential in tissues with high energy demands. This group of creatine deficiency syndromes includes three diseases, two of which are involved in the synthesis of creatine and are autosomal recessive: arginine:glycine aminidino transferase (AGAT) deficiency and guanidinoacetate methyltransferase (GAMT) deficiency. The third is an X-linked condition that occurs due to a creatine transporter (CrT) defect (10). The AGAT deficiency and CrT defect often present with mild epilepsy and EEG abnormalities. GAMT deficiency may be associated with treatment-resistant epilepsy in the form of generalized tonic-clonic, partial, absence, atonic, tonic, or myoclonic seizures or infantile spasms. Typically, patients with creatine deficiency syndromes may present with global developmental delay, intellectual disability, speech impairment, seizures, extrapyramidal movement disorder, and autistic spectrum disorder. Diagnosis is established by measuring levels of creatine and guanidinoacetate in urine, plasma,

or CSF samples. MRS may show a reduced creatine peak. These diseases (mostly AGAT and GAMT) are highly treatable by supplementation of creatine monohydrate at a dose of 350 to 2,000 mg/kg/day.

### Glucose-1-Transporter Deficiency

Glucose-1-transporter (GLUT-1) deficiency is an autosomal dominant disorder due to defect in GLUT-1, the transporter that is exclusively involved in the transport of glucose across the blood–brain barrier and encoded by the *SLC1A* gene (11). Patients typically have an uneventful perinatal course, but in the first 6 months of age, 80% of them develop seizures (focal, absence, myoclonic, partial, astatic); cyanotic spells; abnormal eye movements; and variable degrees of motor, cognitive, and language impairment. At times, a more complex movement disorder including hypotonia, spasticity, ataxia, and dystonia may be seen. Symptoms may aggravate prior to meals and improve with food intake. Diagnosis is established by performing a diagnostic lumbar puncture after a 4- to 6-hour fast. The blood glucose level should be determined immediately before the procedure. A CSF glucose value of less than 40 mg/dl or a CSF:serum glucose ratio of less than 0.35 highly suggests the diagnosis; molecular testing may be done. Treatment using the ketogenic diet helps stop the seizures and overall disease progression and provides for an alternative cerebral energy source.

### Defects of Serine Biosynthesis

Serine, also known as L-serine, is important for cellular proliferation and synthesis of neurotransmitters (D-serine and glycine) as well as synthesis of phospholipids and glycolipids. L-serine is poorly transported across the blood–brain barrier, thus the majority of L-serine is synthesized in the CNS. It follows that enzyme defects in the serine synthesis pathway may precipitate serine deficiency, which has been associated with intractable seizures. The most relevant of these defects is the autosomal recessive 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency (12). In the severe infantile phenotype, the symptoms start perinatally and include congenital microcephaly, intractable seizures, psychomotor and cognitive delays, and spastic quadriplegia, often leading to a misdiagnosis of cerebral palsy. Diagnosis is established by the finding of low serine levels in the CSF and plasma. Treatment often involves supportive care and L-serine supplementation (500 mg/kg/day).

### Phenylketonuria

Phenylketonuria (PKU) is one of the most common aminoacidopathies. Classical PKU is due to an autosomal recessive defect in the hepatic phenylalanine hydroxylase causing toxic accumulations of phenylalanine. Left untreated, PKU causes severe intellectual disability,

behavioral disturbances, psychosis, and seizures in about 25% of the patients (infantile spasms and hypsarrhythmia in infants, myoclonic and tonic-clonic seizures in children). Diagnosis is typically established shortly after birth using the newborn screen. Routine plasma amino acid analysis reveals elevated phenylalanine in untreated patients. Treatment is principally using a phenylalanine-free diet. In contrast, atypical PKU includes a set of very rare diseases with defects in phenylalanine metabolism that do not respond to such a diet.

### Molybdenum Cofactor Deficiency

Molybdenum cofactor deficiency is due to loss of sulfite oxidase function given that molybdenum is critical for the function of the sulfite oxidase enzyme. Symptoms start perinatally with progressive encephalopathy; hypotonia; feeding difficulties; and refractory, partial, myoclonic, and generalized seizures. Diagnosis may be established by findings of elevated urine sulfites and urine S-sulfocysteine along with urine purines and pyrimidines (xanthine and hypoxanthine). Recently, treatment trials using parenteral substitution of a precursor compound cyclic pyranopterin monophosphate seem to yield promising results.

### Adult Disorders

In adults, although rare, it is important to recognize inborn errors of metabolism potentially presenting with late-onset epilepsy with or without other manifestations. These include progressive myoclonic epilepsies (seen in some lysosomal storage diseases, respiratory chain disorders, and Lafora disease), and other epilepsies due to porphyrias, creatine metabolism defects, GLUT-1 deficiency, and Wilson disease (3).

## DIAGNOSTIC APPROACH

As seen in the preceding sections, multiple clues (clinical, radiologic, neurophysiologic) may suggest a possible metabolic epilepsy and trigger a more detailed workup. A list of the common clues seen in neonates, infants and children, and adults may be found in Table 40.6. When suspected, biochemical and, more recently, genetic testing permit establishing a more definitive diagnosis and establishing the correct therapy.

The studies needed to workup the treatable metabolic epilepsies are detailed in Tables 40.7 and 40.8. There have been few attempts at designing a systematic approach to metabolic epilepsies. Figure 40.4 shows a suggested diagnostic approach for adults presenting with epilepsy with concern for an inborn error of metabolism. Figure 40.5 outlines a suggested algorithm to workup and investigate infants and children with suspected metabolic epilepsy.

**TABLE 40.6 Clues to Suspect Metabolic Epilepsies in Various Age Groups**

CLUES IN NEONATES	CLUES IN THE INFANTS AND CHILDREN	CLUES IN ADULTS
Seizures and encephalopathy within 1 to 2 days of birth following normal pregnancy and delivery, absent postpartum complications.	Family history of a sibling dying of an unknown cause	Epilepsy does not match a classical epileptic syndrome
Family history of a sibling dying of an unknown cause or consanguinity in the family	Global psychomotor retardation that can be progressive or regression in milestones with no other potential explanation	Progressive myoclonic epilepsy
Peculiar odor of body fluids	Multisystemic involvement	Association with other neurological or systemic signs
Macrocephaly or microcephaly	Dermatological abnormalities	Family history of similar presentation
History of hydrops fetalis	Characteristic MRI or MRS abnormalities	Seizures are related to eating times
Respiratory distress that cannot be explained by pulmonary or cardiac abnormalities	Episodes of acute metabolic decompensation	Seizures worsen with certain antiepileptic drugs
Cardiomyopathy	Dysmorphism	Unexplained status epilepticus
Organomegaly	Characteristic ophthalmological findings	Unexplained slowing of the background activity on EEG
Dysmorphism	Characteristic EEG abnormalities	Paroxysmal responses during the photic intermittent stimulation at low frequencies on EEG
Hematological abnormalities		
Dermatological abnormalities		
Characteristic MRI or MRS abnormalities		
Characteristic EEG abnormalities		

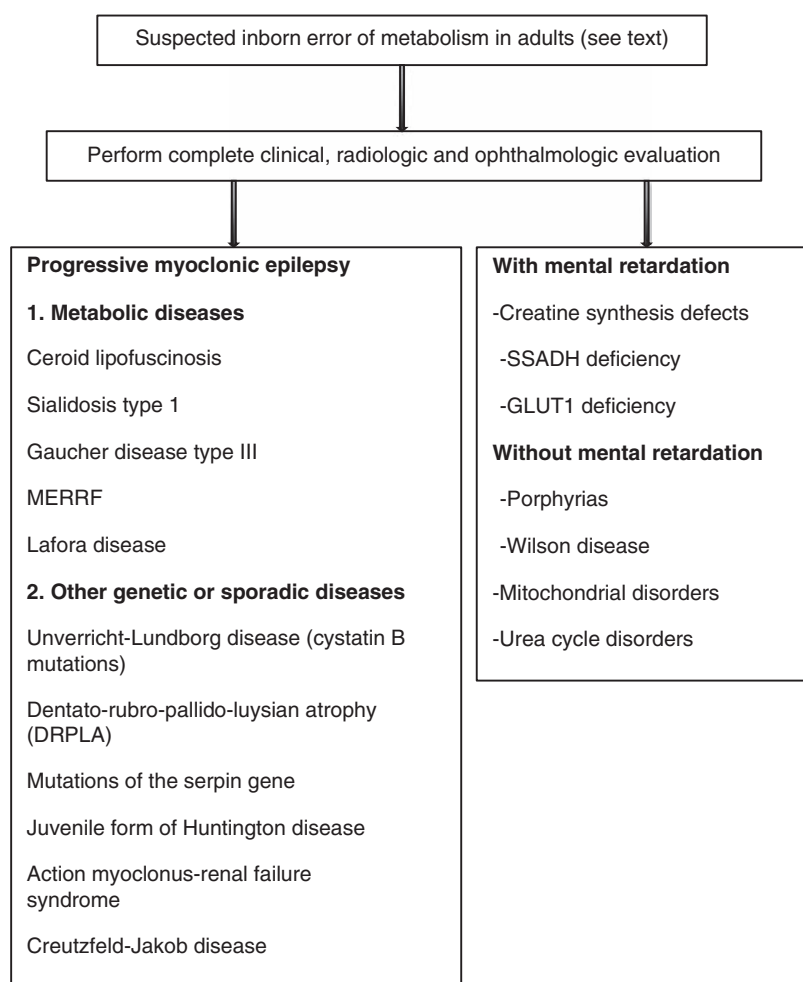
Source: Compiled from Refs. (3) and (13).

**TABLE 40.7 Biomarkers of Common Treatable Metabolic Epilepsies**

METABOLIC EPILEPSY	PLASMA TESTING	URINE TESTING	CSF TESTING	OTHER TESTING
Pyridoxine-dependent epilepsy	Pipecolic acid	Alpha-aminoadipic semialdehyde	Pipecolic acid, Alpha-aminoadipic semialdehyde	Low PLP in CSF
Pyridoxal-phosphate-dependent epilepsy (PNPO deficiency)	–	Vanillactate	Neurotransmitters	Low PLP in CSF
Biotinidase deficiency	Biotinidase activity	Organic acids	–	–
Cerebral folate deficiency/MTHFR deficiency	–	–	Methyltetrahydrofolate	
Glucose-transporter 1 deficiency	Glucose	–	Glucose	CSF:plasma glucose ratio
Guanidinoacetate methyltransferase deficiency	Guanidinoacetate			
Phenylketonuria (classical)	Aminoacids	–	–	
Defects of serine biosynthesis			Aminoacids	
Molybdenum cofactor deficiency type A		S-sulfocysteine, purines and pyrimidines		

Source: Modified from Ref. (2). Dulac O, Plecko B, Gataullina S, Wolf NI. Occasional seizures, epilepsy, and inborn errors of metabolism. *Lancet Neurol.* 2014;13:727–739.





**FIGURE 40.4** Diagnostic approach in an adult patient with suspected metabolic epilepsy.

Source: Modified from Ref. (3). Sedel F, Gourfinkel-An I, Lyon-Caen O, et al. Epilepsy and inborn errors of metabolism in adults: a diagnostic approach. *J Inherit Metab Dis.* 2007;30:846–854.

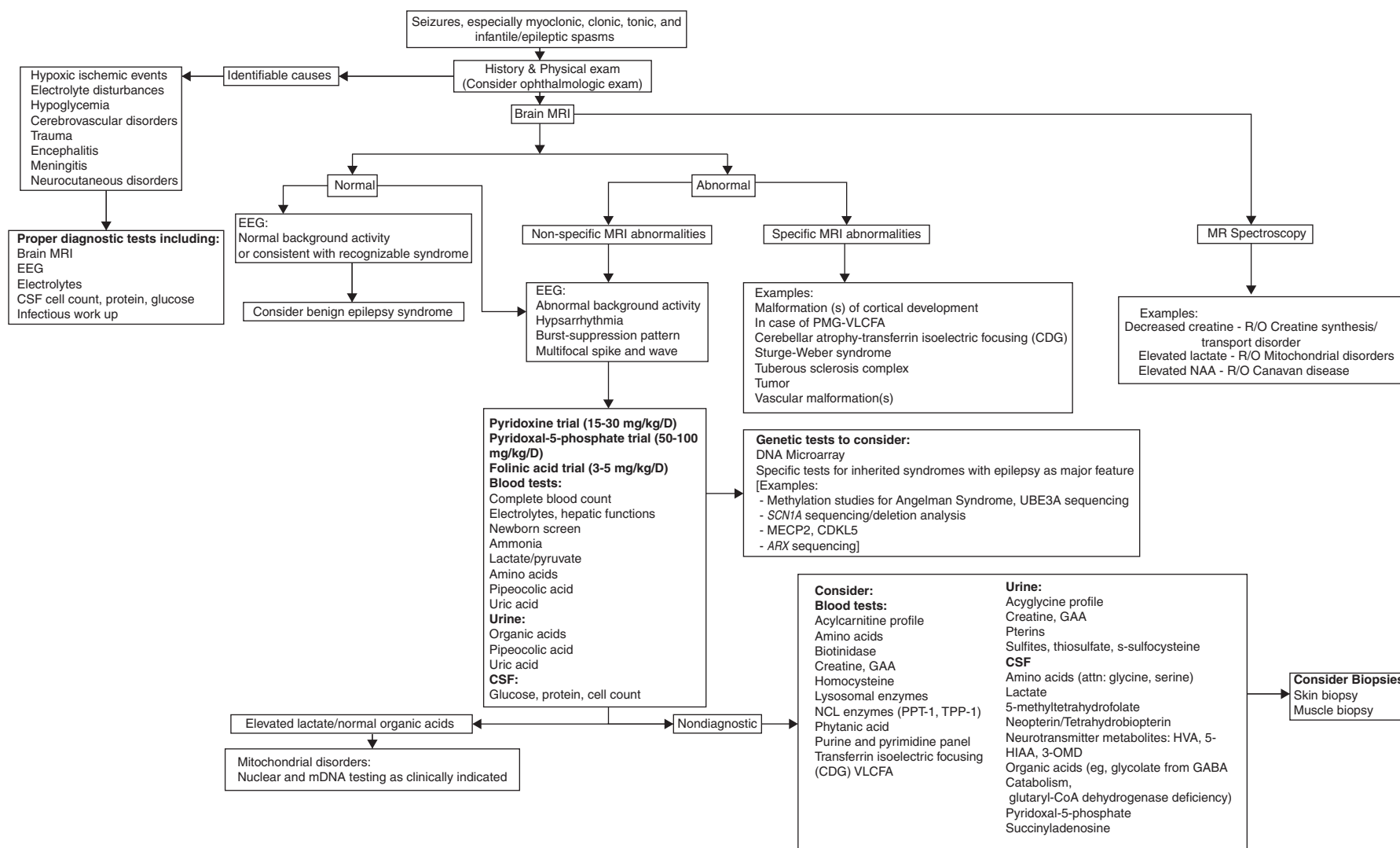
## MANAGEMENT OF COMMON METABOLIC EPILEPSIES

As outlined earlier, some metabolic epilepsies have well-established therapies that often alter disease progression and control the seizure disorder. While many of these diseases are rare, proper identification and management could be life-altering and cost-effective. Unfortunately, the rarity of these diseases often leads to delays in making the diagnosis. Nevertheless, the list of treatable metabolic epilepsies and the awareness about these disorders continue to grow. A list of the common treatable metabolic epilepsies and the respective treatments are found in Table 40.9.

In some instances, no specific treatment is available and supportive treatment of the patient and the caregivers is needed. Treatment of seizures with antiepileptics with or without the use of diet therapy, and addressing other medical needs with the various specialists is expected. It is important to ensure that patients have access to rehabilitation and social services, including physical therapy, occupational therapy, and speech therapy. Working closely with a

metabolic specialist to ensure that the various aspects of a disease are screened for in a periodic fashion is also important. Often, these patients, especially children, may present with metabolic decompensation. Activation of emergency protocols to treat their decompensation needs to be coordinated with the medical team and the metabolic specialist. A great resource on the treatment emergency protocols for the various metabolic diseases may be found at [http://www.orpha.net/consor/cgi-bin/Disease\\_Emergency.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Disease_Emergency.php?lng=EN)

As more treatable metabolic epilepsies are increasingly being discovered, it is important to identify features that suggest a metabolic etiology and initiate a targeted appropriate workup. Focused early treatment often results in not only seizure control but also long-term improvement in developmental and behavioral outcomes. Teaming up with a genetic and metabolic specialist cannot be over-emphasized to help with the diagnosis, management, and surveillance of other family members.



**FIGURE 40.5** Algorithm to identify inherited metabolic epilepsies in children.

Source: Adapted from Ref. (1). Pearl PL. *Inherited Metabolic Epilepsies*. New York, NY: Demos Medical, 2012.

Abbreviations: ARX = Aristaless-related homeobox gene, CDG = Congenital Disorders of Glycosylation, CDKL5 = cyclin-dependent kinase-like 5, GAA = guanidinoacetate, GABA = gamma-aminobutyric acid, 5-HIAA = 5-hydroxyindoleacetic acid, HVA = homovanilic acid, 3-OMD = 3-O-methyldopa, MECP2 = methyl CpG binding protein 2, PMG = Polymicrogyria, PPT1 = palmitoyl-protein thioesterase 1, SCN1A = sodium channel, voltage-gated, type I, alpha subunit gene, TPP1 = tripeptidyl peptidase 1, UBE3A = ubiquitin protein ligase E3A, VLCFA = Very Long Chain Fatty Acids.

**TABLE 40.8. Tiered Approach to the Evaluation of a Metabolic Epilepsy**

TIER ONE	TIER TWO	TIER THREE
Lactate	Pipecolic acid (serum or urine)	CSF amino acids
Ammonia	Alpha amino adipic semialdehyde	CSF lactate
Acylcarnitine profile	Lysosomal storage disease panel	CSF neurotransmitter and vitamin levels, CSF MTHFR...
Free and total L-carnitine	Very-long-chain fatty acid	Urine succinylpurine
Urine organic acids	Urine creatine/guanidinoacetate	Urine glycosaminoglycans
Plasma amino acids	Carbohydrate-deficient transferrin	Copper/Ceruloplasmin
Biotinidase level	Homocysteine	Coenzyme Q10 in leukocytes
+/- Chromosomal microarray	Urine sulfocysteine	Epilepsy gene panel/ whole exome sequencing

**TABLE 40.9 The Suggested Treatments for Common Treatable Metabolic Epilepsies**

METABOLIC EPILEPSY	TREATMENT
Pyridoxine-dependent epilepsy	Pyridoxine +/- pyridoxal phosphate +/- folinic acid
Pyridoxal-phosphate dependent epilepsy (PNPO deficiency)	Pyridoxal phosphate +/- folinic acid
Biotinidase deficiency	Biotin
Cerebral folate deficiency/ MTHFR deficiency	Folate, betaine, methyltetrahydrofolate, methionine...
Glucose-transporter 1 deficiency	Ketogenic diet
Guanidinoacetate methyltransferase deficiency	Creatine supplementation
Phenylketonuria (classical)	Low phenylalanine diet
Defects of serine biosynthesis	L-serine supplementation
Molybdenum cofactor deficiency type A	Cyclic pyranopterin monophosphate

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# Epilepsy and Headaches

*Timothy A. Collins*

Epilepsy and migraine have been discussed as having possible links since the late 1800s. In 1906, Gowers gave a series of lectures titled “On the Borderland of Epilepsy,” with the third lecture devoted to migraine. He expressed the belief that there was some association between migraine, with some patients having migraines earlier in life, transitioning to epileptic fits later in life. He was one of the earliest neurologists to note that aura was a cortically based process, and could be differentiated from “Jacksonian Epilepsy” by the clinical symptoms (1). Since then, various studies and expert opinion have found an association between migraine and epilepsy or have noted a lack of association, depending on the clinical trial.

## EPIDEMIOLOGY

Migraine headache is a common disorder. Lifetime prevalence in women is 12%, and as many as 25% of women have migraine during the reproductive years. In men, the prevalence remains about 6% in all age groups (2). Migraine with aura is seen in a subset of patients with migraine, ranging from 10% to 30% (3).

## ASSOCIATION OF EPILEPSY AND MIGRAINE

In the last 20 years, a number of surveys have attempted to evaluate the association between seizures and migraine. In 1994, a large study using structured phone interviews (3,000 people with epilepsy and their family members) found the incidence of migraine was twice as high in the index family member with epilepsy compared to family members without epilepsy (4). In 1996, a second study by the same authors of adults with epilepsy did not find an association between epilepsy and migraine (5). Migraine has been found to have a higher prevalence in children with epilepsy, with the increased prevalence occurring after the onset of seizures. Other studies have suggested a shared genetic risk for migraine and epilepsy.

Migraine onset appears to occur after onset of seizure in children. Overall patients with idiopathic epilepsy appear to have about twice the risk for migraine compared to the

general population. Conversely, the prevalence of seizures appears to be higher in people with migraine at about 5.9% (range 1%–17%) compared to non-migraine patients. The prevalence of epilepsy in the general population is about 0.5% to 1% (6). Other authors note that the reported prevalence of migraine in patients overlaps the ranges reported in the general population when evaluated by age and gender.

## TERMINOLOGY

The IHS classification of headache disorders (ICHD-II) recognizes two seizure related headache disorders: hemicrania epileptica, and post ictal headache. Hemicrania epileptica is defined as a headache lasting seconds to minutes, with features of migraine, occurring during a partial epileptic seizure. The headache develops synchronously with the seizure, and is ipsilateral to the ictal discharge, and the headache resolves immediately with the seizure. Postictal headache is defined as a headache with features of tension or migraine, developing within 3 hours following the seizure, and resolves within 72 hours. Migralepsy is an older term for a seizure evolving from a typical migraine aura.

The International League Against Epilepsy describes ictal headache as a manifestation of an autonomic seizure. The term “ictal epileptic headache” (IEH) has been used with increasing frequency. IEH is a headache as the only manifestation of an epileptic seizures (7). There are a number of single case reports with onset of headache co-incident with the onset of seizure activity by EEG monitoring. The reported cases typical also have other subtle symptoms including tachycardia and swallowing movements. In a series of 11 patients with headache as the sole manifestation of non-convulsive status, headaches lasted for a prolonged period of time, did not resolve when the seizure activity resolved, and would not meet the ICHD-II criteria for “hemicrania epileptica” (8).

## PATHOPHYSIOLOGY

The pain of migraine headache is a disorder of altered function in the trigeminal sensory nucleus, and the associated cranial vascular structures (often referred to as the trigeminal–vascular



system). Output from the trigeminal nucleus results in release of proinflammatory peptides in the perivascular space in the scalp and meninges including substance P, bradykinin, and calcitonin gene-related peptide (CGRP). This results in plasma protein extravasation from the vessels, a sterile inflammatory response, and sensitization of the surrounding nociceptors. Sensory stimuli result in increased pain perception, followed by central sensitization. The aura of migraine has been linked to spreading cortical depression. In migraine, there is a wave of cortical discharge and increased metabolic activity. This is associated with a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity. The neuronal suppression following this wave is associated with decreased cerebral blood flow, based on decreased metabolic demand.

From a functional viewpoint, increased glutamate release (as seen in mutations associated with familial hemiplegic migraine) facilitates cortical spreading depression, likely due to disruption of the excitatory/inhibitory balance. Increased excitatory amino acids (or decreased reuptake) have been associated with seizures as well (9). Cortical spreading depression moves much slower than propagating seizure activity, suggesting that it spreads through unmyelinated fibers or even cell to cell.

## GENETICS

A number of genes have been associated with familial migraine syndromes, primarily hemiplegic migraine and mitochondrial disorders. Several of the genes associated with familial epilepsy have been found to locate in the same gene as migraine disorders.

### CACNA1A Gene

The *CACNA1A* gene codes for a P/Q type voltage-gated calcium channel. Mutations with gain of function are associated with familial hemiplegic migraine type 1 (FHM1). Patients with hemiplegic migraine have prolonged episodes of migraine headache associated with hemiplegia. Families with FHM1 also have episodic ataxia, and some families have episodic confusion or seizures (9). Episodic ataxia type 2 (EA2) is associated with a mutation in the same sequence as FHM1, and about 50% of patients with episodic ataxia have migraine headaches. Epilepsy is more common in EA2 than in the general population, with an approximate sevenfold increase risk of seizure. Compared to FHM1, the mutation in EA2+epilepsy appears to be a loss of function mutation (10). Other mutations in the *CACNA1A* sequence have been associated with developmental delay, seizures, and hemiplegic migraine. In at least one case, seizures preceded the development of hemiplegic migraine (11).

### ATP1A2 Gene

The *ATP1A2* gene codes for a subunit of the sodium-potassium ATPase. A loss of function mutation causes

familial hemiplegic migraine type 2 (FHM2). In a survey of 30 patients with "sporadic" hemiplegic migraine, 11 patients had de novo mutations in the *ATP1A2* gene. Five of these patients had seizures (11). FHM2 associated with *ATP1A2* mutations have also been associated with familial epilepsy (12).

### SCN1A Gene

The *SCN1A* gene codes for a voltage-gated potassium channel and is associated with FHM. It has been associated with an increased risk for epilepsy (12) and has been associated with myoclonic epilepsy (13).

### SLC1A3 Gene

The *SLC1A3* gene codes for an excitatory amino acid reuptake transporter and results in lower rates of glutamate reuptake. Mutations in the *SLC1A3* gene are associated with episodic ataxia type 6 (EA6). This is associated with episodic ataxia, alternating hemiplegia, and migraine headaches (14).

## Mitochondrial Mutations (15)

### Maternally Inherited Diabetes and Deafness

Maternally inherited diabetes and deafness (MIDD) is due most often to a mutation in tRNA(Leu) or tRNA(Lys) mitochondrial genes. Patients with this condition may also have seizures and migraine headaches.

### Neurogenic Weakness, Ataxia, and Retinitis Pigmentosa

Neurogenic weakness, ataxia and retinitis pigmentosa (NARP) is due to a heteroplasmic transversion m9993T-C in the *ATP6* gene. This is a multisystem disease with ophthalmoplegia, retinitis pigmentosa, ataxia, seizures, and migraine. Electromyography may show evidence of neuropathy and myopathic features but no ragged red fibers (RRF) on biopsy.

### Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

In mitochondrial encephalopathy, lactic acidosis and stroke like episodes (MELAS) initial symptoms are often migraines, vomiting, and seizures. Muscle biopsy shows RRF and increased number of mitochondria. Eighty percent of patients have m3245A > G mutation in the tRNA(Leu) gene.

### Progressive External Ophthalmoplegia

Progressive external ophthalmoplegia (PEO) can be sporadic, autosomal recessive (AR) or dominant (AD). Sporadic PEO is associated with a large mtDNA deletion that is often found only in muscle tissue. AR and AD forms of PEO are associated with four mutations. *POLG1* (catalytic subunit of mtDNA specific polymerase gamma), *PEO1* (encodes mtDNA helicase "twinkle"), *SLC25A4* (muscle heart specific

mitochondrial adenine nucleotide translocator 1 [ANT1]), and *ECGF1* encoding thymidine phosphorylase. *POLG1* mutations are the most common causes of familial PEO. Clinically, patients with PEO have ophthalmoplegia, and may have neuropathy (axonal) migraine headaches, seizures, and movement disorders including ataxia and parkinsonism.

## TREATMENT

Episodic migraine is expected to occur in patients with seizure disorders, based on gender specific incidence of migraine discussed earlier. It can be treated with similar medications used for patients without a seizure disorder.

### Acute Migraine Therapy

The triptans (see Table 41.1) have been standard therapy for acute migraine for 20 years, and are not associated with an appreciable risk for triggering seizures. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for acute migraine therapy, with a preference for NSAIDs with longer duration of action (naproxen preferred over ibuprofen, for example). Older medications containing ergotamines remain effective, but cannot be combined with triptans due the increased risk of vasospasm. Butalbital-containing products should

be avoided in patients with seizure disorder. Butalbital as a barbiturate may result in drug interactions with older anti-convulsants, and abrupt withdrawal of butalbital can trigger seizures or delirium.

### Migraine Prophylaxis

Patients having migraines more than 2 days per week should be offered prevention medications (see Table 41.2). Propranolol and similar beta blockers, along with calcium channel receptor blockers such as verapamil (or flunarizine outside the United States), would not be expected to alter seizure frequency or interfere with seizure therapy. Low-dose tricyclic antidepressant medications may be used cautiously but can theoretically lower seizure threshold, and may not be appropriate in patients with poorly controlled epilepsy. One form of botulinum toxin (Botox, Allergan) is FDA approved for prophylaxis of chronic daily migraine. Botulinum toxin is mainly peripherally acting, and would not be expected to interfere with standard therapy for seizure disorder.

Two anticonvulsants, topiramate and valproate, are FDA approved in the United States for migraine prevention. While topiramate has minimal interactions with other anticonvulsants, valproate may affect metabolism of other medications, and should be used carefully especially in patients on lamotrigine. Valproate is contraindicated in patients with seizures due to mitochondrial disease. There are a very small number of studies evaluating the

**TABLE 41.1 Medications for Acute Migraine Treatment**

CLASS		
TRIPTANS	DOSE RANGE	COMMENTS
Sumatriptan	50–100 mg	Injection, nasal preparations also available
Zolmitriptan	2.5–5 mg	Nasal version available
Rizatriptan	5, 10 mg	
Eletriptan	20, 40 mg	
Almotriptan	12.5 mg	
Frovatriptan	2.5 mg	
Naratriptan	12.5 mg	
Sumatriptan + Naproxen	80/500 mg	
Ergotamines	4 mg	Nasal spray, combined with caffeine
Dihydroergotamine	1 mg	Intravenous
NSAIDS		
Naproxen	500–1,000 mg	
Ibuprofen	800 mg	
Diclofenac	50 mg	Rapidly dissolving powder
Indomethacin	50–150 mg	

**TABLE 41.2 Migraine Prophylaxis**

ANTIDEPRESSANTS	DOSE RANGE PER DAY
Amitriptyline	25–100 mg
Nortriptyline	10–100 mg
ANTICONVULSANTS	
Topiramate	100–150 mg
Valproate	500–1,500 mg
ANTIHYPERTENSIVES	
Propranolol	80–240 mg
Verapamil	120–480 mg
Lisinopril	5–15 mg
ONABOTULINUMTOXIN A	
MEDICATIONS WITH LIMITED PUBLISHED DATA	
Gabapentin	800–2400 mg
Pregabalin	150–600 mg
Levetiracetam	1000–3,000 mg
Duloxetine	30–60 mg
Zonisamide	300–400 mg

effectiveness of gabapentin and leviteracetam for migraine prophylaxis, but in occasional patients these medications may be effective for migraine prevention. There are no randomized trials evaluating the effectiveness of pregabalin or zonisamide for migraine prevention, but these medications are often used in tertiary headache centers and may be effective.

Bupropion and tramadol both can provoke seizures in patients without epilepsy, and should be avoided in patients with seizure disorder.

Migraine and seizures are closely related, with a higher-than-expected incidence of migraine headache in patients with seizures. The larger studies suggest there is a slightly higher risk of seizures in patients with migraine. While the genetics of sporadic migraine are unclear at this point, there is clear overlap between the genetics of hemiplegic migraine, familial seizures, and episodic ataxia disorders. The presence of hemiplegic migraine in a seizure patient should prompt testing for a genetic cause, as well as an evaluation of the family for other episodic disorders, including mitochondrial mutations. The terminology of headache related to seizure is currently evolving. The older “migralepsy” should be abandoned, as current evidence suggests that this is a partial seizure manifesting as headache followed by more generalized seizure activity. IEH is a more appropriate diagnosis in this situation. Headache in patients with seizures should be treated with standard therapy based on headache symptoms, within the constraints of their current treatment for seizures.

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# Epilepsy and Sleep

*Erick N. Viorritto and Sujay M. Kansagra*

Even before the advent of EEG in the early twentieth century, clinical observation had borne out a connection between epilepsy and sleep. It was observed that nocturnal seizures were more likely to occur at specific times during sleep, and that daytime seizures may disrupt sleep the following night (1). Once EEG allowed for a more rigorous study of both epilepsy and sleep physiology, the complexity of that relationship became evident.

Epilepsy and sleep are interrelated in a variety of ways. Seizures disrupt the normal architecture and physiology of sleep, and the manifestations of many epilepsy syndromes display specific patterns related to the patient's sleep-wake cycle, as summarized in Table 42.1. Furthermore, sleep disorders are often comorbid with epilepsy, which may exacerbate the patient's epilepsy and complicate treatment. Finally, therapies for epilepsy (both pharmacologic and nonpharmacologic) may impact an individual's normal sleep physiology, and therapies for sleep disorders may affect seizure control in the patient with epilepsy.

## THE EFFECT OF SLEEP ON EPILEPSY

Sleep consists of two easily distinguishable states: rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep. NREM sleep is further divided into three stages—N1, N2, and N3 sleep. There is increasing neuronal synchronicity on EEG as one goes from light N1 sleep to N3 sleep (termed "slow-wave sleep"). Clinically, there are two peaks during the night in which seizures are most common. These occur between 9 p.m. and 11 p.m., and then later in the night between 3 a.m. and 5 a.m. (1). When examined in relation to the EEG, most sleep-related seizures occur during NREM sleep, where synchronous neuronal activity may serve to facilitate the generation and propagation of seizures. This interpretation, however, does not explain why sleep-related seizures are more common during stage N2 sleep (61%–68%) compared to the more synchronous N3 stage (9%–14%) (2). It is possible that the thalamocortical hypersynchrony that is evident during stage N2 sleep, as manifest by the generation of sleep spindles and K-complexes on the EEG, may promote interictal spikes and epileptic activity

(3). REM sleep appears to be relatively protective against seizures, with most studies showing that less than 1% of sleep-related seizures occur during this stage. This may be due to the relatively desynchronized activity that is seen during REM sleep (4). While seizures in REM sleep are rare, epileptiform discharges during REM sleep may be the most accurate in helping to localize an epileptogenic focus for epilepsy surgery.

Sleep deprivation is a fairly standard activating procedure used to increase the yield for capturing interictal abnormalities and seizures on EEG. Sleep deprivation activates interictal discharges in one-third of patients with epilepsy, and the yield in patients with sleep-related epilepsies may be much higher (1). Sleep deprivation also likely has direct effects on cortical excitability, serving to lower the seizure threshold (2).

## Focal Epilepsies

It has been observed since the nineteenth century that there is a substantial cohort of patients with epilepsy who only have seizures during sleep. According to one study, such "pure sleep epilepsies" occurs in about 6% of patients with epilepsy. A larger group, making up approximately 10% of epilepsy patients, has seizures predominantly during sleep with only occasional daytime seizures (2). About 80% of the pure sleep epilepsies are focal, with idiopathic focal epilepsy more likely to have seizures restricted to sleep than to lesional focal epilepsy (2).

Idiopathic focal epilepsies, such as benign epilepsy of childhood with centrotemporal spikes (BECTS), display focal-onset seizures occurring predominantly during sleep. In 70% to 80% of cases, the seizures are exclusive to sleep (2). A neurophysiologic feature of this syndrome is the marked activation of interictal discharges during drowsiness and light NREM sleep (2). Studies have shown that in up to one-third of patients with BECTS, the interictal discharges themselves are seen only during sleep (1).

Early-onset childhood epilepsy with occipital spikes (Panayiotopoulos syndrome) also presents with focal-onset seizures predominantly occurring during sleep, with



prominent autonomic fluctuations, behavioral disturbances, and significant emesis. Two-thirds of the seizures begin during sleep, and they can last over an hour in a quarter of cases (5). As in BECTS, a hallmark of this epilepsy is the emergence of interictal discharges during NREM sleep (2).

Most patients with autosomal dominant nocturnal frontal lobe epilepsy syndrome (ADNFLE) likewise present with seizures that occur exclusively during sleep (2). This syndrome is characterized by nocturnal clusters of brief, stereotyped motor seizures during sleep. There is typically a maintenance of consciousness during the seizures and minimal or absent postictal confusion. The foci for these seizures may be deep, and thus they may lack interictal and ictal EEG findings, leading to their misdiagnosis as a parasomnia or sleep disorder (6).

Symptomatic focal epilepsies from the frontal lobe and temporal lobe can be sleep-related and produce seizures that occur predominantly out of sleep. The most commonly encountered of these is temporal lobe epilepsy, owing to the relative frequency of this epilepsy type; frontal lobe foci however have the greatest likelihood of displaying a sleep-related pattern. Approximately 61% of frontal lobe seizures arise from sleep, compared to 11% of temporal lobe seizures (7). If over 90% of a patient's seizures arise out of sleep, the patient is considered to have nocturnal frontal lobe epilepsy (NFLE) or, less commonly, nocturnal temporal lobe epilepsy (NTLE), depending on the location of the foci (2). Evidence suggests that NTLE may carry a better prognosis following surgical resection than temporal lobe epilepsies in which seizures are not restricted to sleep (7).

Interictal discharges in symptomatic focal epilepsies are facilitated by NREM sleep. Discharges can also be seen during REM sleep with less frequency. These interictals tend to show a more restricted field, and studies suggest that these REM-related interictal discharges may be a more reliable indicator of the epileptic focus than interictal discharges seen during wakefulness or NREM sleep (2,4).

### Generalized Epilepsies

Most idiopathic generalized epilepsies present with seizures primarily during wakefulness, although a pattern of seizures related to sleep still exists. This category includes the "awakening epilepsies," in which seizures predominantly occur within the first two hours after the patient wakes up (8). This is seen in the cases of juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures on awakening. Sleep deprivation tends to elicit seizures in patients with these syndromes. Interictal generalized discharges are seen most frequently during NREM sleep and least frequently during REM sleep, and may be seen in association with K-complexes on the EEG (2). Fewer than 10% of patients with idiopathic generalized epilepsy present with a pure sleep epilepsy (9). Symptomatic generalized epilepsies may present with seizures during both wakefulness and sleep, although again a clear sleep-related pattern can be seen. In Lennox-Gastaut syndrome, multiple seizure

types can be seen during wakefulness, including generalized tonic-clonic, tonic, atonic, myoclonic, and atypical absence seizures. Tonic seizures during NREM sleep can be seen in over 90% of patients, and are accompanied by paroxysmal fast activity on EEG. Interictal spike-wave discharges also become more prominent during NREM sleep where runs of generalized polyspike discharges and rhythmic bursts of fast activity may be seen (1). In contrast, only 2% to 5% of the infantile spasms associated with West syndrome occur during sleep, instead occurring in clusters upon awakening. The interictal hypsarrythmia EEG pattern in West syndrome, however, is most prominent during early NREM sleep, and in some patients may only be evident during NREM sleep (1,2).

### Epileptic Encephalopathies

Clear sleep-related EEG changes are seen in both continuous spike-wave during slow-wave sleep (CSWS) and Landau-Kleffner syndrome (LKS). In both disorders, sleep is accompanied by near-continuous, epileptiform activity on the EEG. In the waking state, both disorders are marked by deterioration in neurocognitive function. CSWS is associated with nocturnal focal motor seizures and occasionally absence seizures during wakefulness, while LKS may or may not be accompanied by clinical seizures (2).

### EFFECT OF EPILEPSY AND SEIZURES ON SLEEP

There is a reciprocal relationship between sleep and epilepsy: while it is clear that sleep plays a role in seizure frequency, so too do seizures and epilepsy affect an individual's sleep. These changes are likely due to multiple factors. There may be an effect from the underlying pathological mechanism of the epilepsy on sleep, independent of whether or not seizures are occurring. There are also changes in nocturnal sleep that can be seen as a result of either nocturnal seizures or diurnal seizures in the period preceding sleep. Finally, many antiepileptic drugs (AEDs) and therapies also affect sleep.

#### The Effect of Epilepsy and Seizures on Sleep Continuity and Architecture

Epilepsy appears to have an impact on sleep continuity and sleep architecture independent of the presence of seizures on a given night. This appears to predominantly involve an increase in wake time after sleep onset (WASO) and an increased number of awakenings on nights in which seizures did not occur (1). This has been hypothesized to be due to aberrant GABA release. It also appears that this effect is more prominent in temporal lobe epilepsy compared to primary generalized epilepsy (10). In temporal lobe epilepsy, nocturnal seizures are also associated with independent changes in sleep architecture, with increased WASO, decreased sleep efficiency, decreased REM sleep, decreased N2 sleep, decreased N3 sleep, increased N1 sleep, and increased

**TABLE 42.1 Sleep-Related Characteristics of Epilepsies**

EPILEPSY TYPE	SLEEP-RELATED FEATURES	EPILEPSY SYNDROMES
Idiopathic generalized	Seizures upon awakening. Sleep deprivation elicits seizures. Interictal discharges are most prominent during NREM sleep.	Juvenile myoclonic epilepsy Epilepsy with generalized tonic-clonic seizures on awakening
Symptomatic generalized	Seizures during sleep and wakefulness (LGS) or upon awakening (West syndrome). Interictal abnormalities most prominent during NREM sleep.	Lennox-Gastaut syndrome West syndrome
Idiopathic focal	Seizures occur predominantly or exclusively during sleep. Interictal abnormalities are activated by drowsiness and NREM sleep.	Benign childhood epilepsy with centrotemporal spikes (BECTS) Benign childhood epilepsy with occipital paroxysms Autosomal dominant nocturnal frontal lobe epilepsy syndrome (ADNFLE)
Symptomatic focal	Epilepsies from the frontal lobe are more likely to be nocturnal than those from the temporal lobe. Interictal discharges are facilitated by NREM sleep, particularly slow wave sleep.	Frontal lobe epilepsy Temporal lobe epilepsy Nocturnal frontal lobe epilepsy Nocturnal temporal lobe epilepsy

next-day drowsiness. On the night following a diurnal temporal lobe seizure, decreased REM sleep is also seen, without the changes in WASO, sleep efficiency, and amounts N1, N2, and N3 sleep seen after nocturnal seizures (11).

### Effect of Epilepsy Therapies on Sleep

#### *Antiepileptic Drugs*

Isolating the effects of epilepsy on sleep architecture may be confounded by the effects of AED therapy. Most studies of sleep in patients with epilepsy are done while the patient continues AED therapy. For some agents, the effects on sleep have been studied, and are summarized in Table 42.2. For most, however, there are no reliable data on how they independently affect sleep architecture.

Phenytoin is known to disrupt sleep by increasing N1 sleep at the expense of N3. Valproate and ethosuximide also increase N1 sleep. Gabapentin is unusual in that it appears to increase N3 sleep and REM sleep, and may actually have a beneficial effect on sleep in patients with epilepsy (12). Pregabalin and levetiracetam increase N3 sleep but decrease REM. Benzodiazepines cause a decrease in slow-wave sleep and REM. This decrease in slow-wave sleep likely explains the effectiveness on benzodiazepines on the NREM parasomnias that tend to occur out of slow-wave sleep. Carbamazepine and lamotrigine have so far not been shown to have a significant effect on sleep stages. Insomnia is a side effect in a minority of patients taking lamotrigine and felbamate.

AEDs may also exacerbate underlying sleep disorders. Benzodiazepine and barbiturates may exacerbate obstructive sleep apnea (OSA) by decreasing upper airway tone and

suppressing arousal mechanisms. Medications that are associated with increased weight may also lead to worsening of OSA. Isolating sleep changes secondary to these effects from primary medication effects on sleep remains an understudied area.

#### *Nonpharmacologic Therapies: Vagus Nerve Stimulator and Ketogenic Diet*

Vagus nerve stimulator treatment for epilepsy may decrease daytime sleepiness in patients with epilepsy, as evidenced by a statistically significant increase in mean sleep latency on the mean sleep latency test (MSLT) from 6.4 minutes to 9.8 minutes (13). There is also evidence however that vagus nerve stimulation may exacerbate sleep apnea in patients with OSA syndrome, via central and peripheral mechanisms (13). Decreased airflow is seen on polysomnography during VNS activation, with maintenance of respiratory effort, suggesting an obstructive etiology. In most cases, this effect appears to be mild; in a small study of 16 patients with epilepsy and VNS placement, there was an increase in the number of respiratory events per hour (apnea-hypopnea index, or AHI) in all patients. The AHI rose to above 5 per hour (the threshold for mild OSA in adults) in five patients, although two of those patients did have evidence of preexisting OSA (14).

Care must be taken when scoring events during VNS activation. VNS activation is typically obvious due to artifactual increase in chin EMG signal during a polysomnogram. Stimulation of vagus nerve afferent fibers is known to cause physiologic changes in respiration. Vagus nerve afferents are important in the brainstem's control of respiration. Stretch-sensitive mechanoreceptors within the lungs send their signal to the brainstem via the vagus nerve. VNS

**TABLE 42.2 Effects of Antiseizure Medications on Sleep Architecture**

MEDICATION	EFFECT ON SLEEP
Benzodiazepines	Decrease slow-wave sleep Decrease REM sleep Decrease sleep latency
Carbamazepine	No proven significant effects on sleep architecture
Ethosuximide	Increase stage 1 sleep May cause insomnia
Gabapentin	Increase slow-wave sleep Increase REM sleep Increase sleep efficiency
Lamotrigine	No proven significant effects on sleep architecture May cause insomnia
Levetiracetam	Increase slow-wave sleep Decrease REM sleep
Phenytoin	Increase stage 1 sleep Decrease slow-wave sleep
Pregabalin	Increase slow-wave sleep Decrease REM sleep
Topiramate	No proven significant effects on sleep architecture
Valproate	Increase stage 1 sleep
Zonisamide	No proven significant effects on sleep architecture

activation increases this afferent signal and may cause the brainstem to decrease the amplitude of each breath, since the brainstem falsely interprets the lungs to be excessively expanded. This may be misinterpreted as an obstructive event, when in reality it is a normal physiologic response to vagus nerve stimulation.

A small study of 18 children on the ketogenic diet for refractory epilepsy showed a significant decrease in total sleep time, with preserved N3 sleep and increased REM sleep, as well as decreased daytime sleepiness and a further increase in REM sleep at 12-month follow-up, indicating an overall improvement in sleep quality (15). These children also showed a significant decrease in seizure frequency and severity, making it unclear whether the improvements in sleep are independent from the improvements in their epilepsy.

### EFFECT OF SLEEP DISORDERS AND MEDICATIONS ON EPILEPSY

Just as epilepsy can influence an individual's sleep, some sleep disorders may impact seizure control in individuals with epilepsy, either through disruption of nighttime sleep, or because the medications used to treat sleep disorders affects the seizure threshold.

### Obstructive Sleep Apnea

There is evidence that effective treatment of OSA can lead to improved seizure control in the absence of medication changes. A study comparing patients with epilepsy on continuous positive airway pressure (CPAP) versus a control group on sham-CPAP showed a response rate (defined as a 50% or greater reduction in seizure frequency) of 28% with CPAP versus 15% with sham-CPAP (13). A retrospective study of 41 patients with epilepsy and OSA treated with CPAP showed a statistically significant decrease in seizure frequency in the CPAP-compliant group (1.8 seizures per month to 1 per month) versus the CPAP-non-compliant group (2.1 per month to 1.8 per month) after at least 6 months of treatment. Fifty-seven percent of the CPAP compliant patients were seizure-free at follow-up, as compared to 23% of the CPAP noncompliant patients (16). An uncontrolled confounder in this study, however, was compliance with AEDs, which was not assessed, and likely differed between the two groups. Similar to adult studies, children with OSA and epilepsy also have improvement in seizure frequency after undergoing tonsillectomy and adenoidectomy to treat their OSA.

There is evidence that epilepsy may be an independent risk factor for OSA. While AEDs such as benzodiazepines and barbiturates can exacerbate underlying airway obstruction, and medications such as valproate can contribute to weight gain, there also appears to be an underlying increased risk for OSA in patients with epilepsy (13). First-line therapy for OSA in adults is continuous positive airway pressure (CPAP). Treatment of underlying OSA with CPAP can lead to decreased daytime sedation, which may allow for further increases in AED doses (for which sedation is often the dose-limiting side effect).

### Other Sleep Disorders

Other sleep disorders can also coexist with epilepsy, including restless legs syndrome, periodic limb movement disorder, insomnias, and central hypersomnias. To date, there is little research on the implications of these comorbid sleep disorders for epilepsy and seizure control. Except in cases in which medications with known seizure-suppressing properties may be used for sleep disorders (such as benzodiazepines in the treatment of insomnia or parasomnia), there are little rigorous data examining the effects of sleep disorder therapies on comorbid epilepsy. The occurrence of seizures following chronic benzodiazepine withdrawal is well recognized. There are a number of case reports of withdrawal seizures following cessation of the nonbenzodiazepine hypnotic zolpidem in the setting of zolpidem dependency and chronic use of the medication at very high doses (17).

### Stimulants and Wakefulness-Promoting Medications

The use of stimulant medication such as methylphenidate and amphetamine/dextroamphetamine in individuals with

epilepsy has raised some concerns that these medications may lower the seizure threshold. This most often arises in the setting of treating comorbid attention deficit hyperactivity disorder; however, these medications are also commonly prescribed for the treatment of hypersomnias such as narcolepsy and idiopathic hypersomnia. Multiple studies support the conclusion that stimulant medication does not significantly lower the seizure threshold in children with epilepsy (18). Similarly, the use of nonstimulant wakefulness-promoting medications such as modafinil and armodafinil in individuals with epilepsy has been approached with caution. These medications, too, do not appear to significantly lower the seizure threshold in patients with epilepsy (19).

### Melatonin

Melatonin is commonly used in a variety of sleep disorders. Because melatonin is available over the counter as a supplement, many individuals take it without the advice or recommendation of their physician and may not mention it when queried about their medications. A review of the existing literature on melatonin and seizure frequency found no consistent pattern of seizure improvement or worsening with melatonin therapy (20). This review included three double-blind randomized controlled trials, in which two showed no statistically significant change in seizure frequency, and one showed a significant decrease in seizures. Less rigorously conducted studies, however, showed inconsistent results, including reports of increased seizure frequency in patients on melatonin. At this time, adequate data do not exist to answer this definitively, and further study is needed (20).

The interactions between epilepsy and sleep have been recognized for more than a century. More recently the complexity of this relationship has been elucidated. Epilepsy can affect sleep even without seizures occurring during the night. Certain epilepsy syndromes occur at certain time points in the sleep–wake cycle. Sleep disruption and disorders can have a negative effect on seizure control. Many AEDs can affect sleep and sleep-related medications may impact seizure control.

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# Sudden Unexpected Death in Epilepsy

*Abeer J. Hani and Rodney A. Radtke*

Mortality in people with epilepsy can be attributed to one of three causes: epilepsy-related causes, causes related to the underlying etiology of the epilepsy, and causes unrelated to the epilepsy or its underlying etiology. The epilepsy-related deaths include seizure-related deaths, treatment-related deaths, status epilepticus, and sudden unexpected death (SUDEP). Among these causes, SUDEP remains an important cause of premature death in epilepsy patients. The reported incidence of SUDEP has varied widely depending on cohorts included. A systemic review (1) of available studies yielded the following statistics. Assuming an overall epilepsy prevalence of 7.1 per 100,000 population, the crude annual incidence of SUDEP is estimated at 1.16 per 1,000 persons with epilepsy. Epilepsy onset at the age of 1 year incurs a lifetime risk of SUDEP of 8% by 70 years of age, whereas epilepsy onset at the age of 30 years yields a corresponding risk of 4.6%. The lowest incidence of SUDEP is reported in population-based incidence cohorts with higher incidence noted in those with refractory epilepsy (2). The risk among patients with presumably chronic and often refractory epilepsy has been reported as 1.1–5.9 per 1,000 person-years. The highest risk has been reported among epilepsy surgery candidates or patients who continue to have seizures after surgery with estimated risk of 6.3–9.3 per 1,000 person-years. In the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS), the risk of SUDEP was 1.2 per 10,000 video EEG (vEEG) monitorings (3).

Despite the desire to improve the understanding of SUDEP, the discussion of SUDEP in the clinical setting continues to be a great challenge to physicians and patients alike. In this chapter, an overview of the definition of SUDEP, mechanisms involved and risk factors of SUDEP will be provided. This is then followed by a discussion of the possible methods to prevent SUDEP. Finally, an approach to counseling patients about SUDEP will be suggested.

## DEFINITION AND CLASSIFICATION OF SUDEP

The classification and diagnosis of SUDEP is a challenging task, given the unpredictable occurrence, often in unwitnessed settings, and often with lack of complete autopsies

examinations. As such, there has been an effort to improve and standardize the definition of SUDEP. In 1997, two complementary definitions of SUDEP were proposed (Table 43.1) (4,5). The classic definition of SUDEP has been a “sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death (4).” If a postmortem examination finds no other causes of death, the case would be considered a definite SUDEP. If autopsy were not performed, it would be considered a probable SUDEP.

In 2012, a unified definition and classification of SUDEP was suggested (Table 43.2) (6). The aim of the unified definition was to expand the definition of SUDEP and to clarify some of the definitions as well as to provide a framework to define SUDEP even in the absence of all the data surrounding the circumstances of death in epilepsy. The updated definition of SUDEP now is a “sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration  $\geq 30$  minute or seizures without recovery in between), in which postmortem examination does not reveal a cause of death.” The concept of SUDEP plus has been introduced also to identify situations whereby evidence indicated that a preexisting condition could have contributed to the death in addition to SUDEP. An example of a SUDEP plus case would be the unwitnessed sudden death in an epilepsy patient with known long QT-syndrome and with negative postmortem examination. Different categories of SUDEP have been suggested, including definite SUDEP /SUDEP plus, probable SUDEP/ SUDEP plus, possible SUDEP, near-SUDEP/SUDEP plus, not SUDEP and unclassified. Selected examples of each of these types can be found in Table 43.2.

## MECHANISMS UNDERLYING SUDEP

The putative mechanisms underlying SUDEP continue to be a subject of evaluation and research. Periictal alteration

TABLE 43.1 The 1997 Definitions of SUDEP

NASHEF 1997 DEFINITION OF SUDEP	ANNEGERS 1997 DEFINITION OF SUDEP
Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death.	<p>Criteria for diagnosis of SUDEP:</p> <ul style="list-style-type: none"> <li>■ The victim had epilepsy, defined as recurrent unprovoked seizures</li> <li>■ The victim died unexpectedly while in a reasonable state of health</li> <li>■ The death occurred “suddenly” (in minutes), when known</li> <li>■ The death occurred during normal activities (eg, in or around bed, at home, and at work) and benign circumstances</li> <li>■ An obvious medical cause of death was not found</li> </ul> <p>Classification of SUDEP:</p> <ul style="list-style-type: none"> <li>■ Definite SUDEP: meets all criteria, with postmortem examination</li> <li>■ Probable SUDEP: meets all criteria, but lacks postmortem data</li> <li>■ Possible SUDEP: SUDEP cannot be ruled out, but there is insufficient evidence regarding the circumstances of the death and no postmortem report available</li> <li>■ Unlikely/Not SUDEP: cause of death clearly established, or the circumstances make SUDEP highly improbable</li> </ul>

Source: Adapted from Refs. (4) and (5).

TABLE 43.2 Unified 2012 Definition and Classification of SUDEP

SUDEP TYPE	DEFINITION	EXAMPLES
Definite SUDEP <sup>a</sup>	Sudden, <b>unexpected</b> , witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥ 30 minute or seizures without recovery in between), in which postmortem examination does not reveal a cause of death	Witnessed sudden death in sleep or during activity including exercise in an epilepsy patient, no seizure; negative postmortem examination
Definite SUDEP Plus <sup>a</sup>	Satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death	Cardiorespiratory arrest after habitual seizure in an epilepsy patient; postmortem examination shows coronary artery atheroma but no evidence of myocardial infarction
Probable SUDEP/ Probable SUDEP Plus <sup>a</sup>	Same as Definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death	Epilepsy patient, no other relevant preexisting conditions; dead in bed in the morning, benign circumstances; no postmortem examination
Possible SUDEP <sup>a</sup>	A competing cause of death is present	Epilepsy patient, no other relevant preexisting conditions; dead in water but not submersed, benign circumstances; postmortem examination
Near-SUDEP/ Near-SUDEP Plus	A patient with epilepsy survives resuscitation for more than 1 hour after a cardiorespiratory arrest that has no structural cause identified after investigation	Epilepsy patient; cardiorespiratory arrest after witnessed seizure, resuscitated but dies within a few days or weeks; negative postmortem examination

(continued)

TABLE 43.2 Unified 2012 Definition and Classification of SUDEP (*continued*)

SUDEP TYPE	DEFINITION	EXAMPLES
Not SUDEP	A clear cause of death is known	Epilepsy patient; cardiorespiratory arrest after habitual seizure, resuscitated but dies after 5 days; postmortem examination shows large myocardial infarction
Unclassified	Incomplete information available; not possible to classify	—

<sup>a</sup> If a death is witnessed, an arbitrary cutoff of death within 1 hour from acute collapse is suggested.

Source: Adapted from Ref. (6). Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia*. 2012;53:227–233.

of respiratory function, cardiac arrhythmias, and alterations in sleep and autonomic function as well as various genetic factors have been implicated in the mechanisms underlying SUDEP (Figure 43.1). Knowledge of these mechanisms will help guide the development of strategies to prevent SUDEP.

### Respiratory Mechanisms

Several human and animal studies have implicated pathophysiologic respiratory alterations during seizures with the risk for SUDEP (7). It has been found that seizure-related hypoxemia and hypercapnia occur in about one-third of patients with focal or generalized seizures. Periictal oxygen desaturations were found to be present more in males,

temporal lobe seizures, right hemispheric seizures, and with seizures that spread to the contralateral hemisphere. Ictal central apneas were found to be more common than obstructive apneas. The mean duration of a periictal apnea was found to be about 49 seconds, whereas the elevations of end-tidal carbon dioxide were found to last about 7 minutes after a seizure. This indicates the possible contribution of other mechanisms, including pulmonary shunting or transient pulmonary edema in the respiratory alterations following a seizure. This has been validated by postmortem findings of pulmonary edema as well as research using animal models. It has also been found that oxygen desaturation lasts longer and is more severe when seizures are followed by postictal generalized EEG suppression. Findings from the MORTEMUS study suggested the following possible sequence for 10 patients who succumbed to SUDEP while undergoing vEEG monitoring. Rapid breathing (18–50 breaths per minute) developed after a secondary generalized tonic-clonic seizure, followed within 3 minutes by transient or terminal cardiorespiratory dysfunction. When transient, this dysfunction was followed by terminal apnea occurring within 11 minutes of the end of the seizure, followed by cardiac arrest (3).

On another note, projections from the limbic regions innervate brainstem areas that control respiratory function. Stimulation of the insula, temporal pole, anterior hippocampus, and anterior cingulate cortex has been observed to cause apnea. Hence, seizures involving these limbic regions may be associated with respiratory disturbances that could predispose to SUDEP.

### Autonomic and Cardiac Mechanisms

There has been abundant research on possible cardiac mechanisms underlying SUDEP (8). For a complete list of possible cardiac mechanisms investigated, please refer to Table 43.3. Multiple mechanisms are related to neurocardiac channelopathies. Long and short QT syndromes are often seen with associated sodium and potassium channel mutations. These syndromes often cause abnormal neuronal repolarization

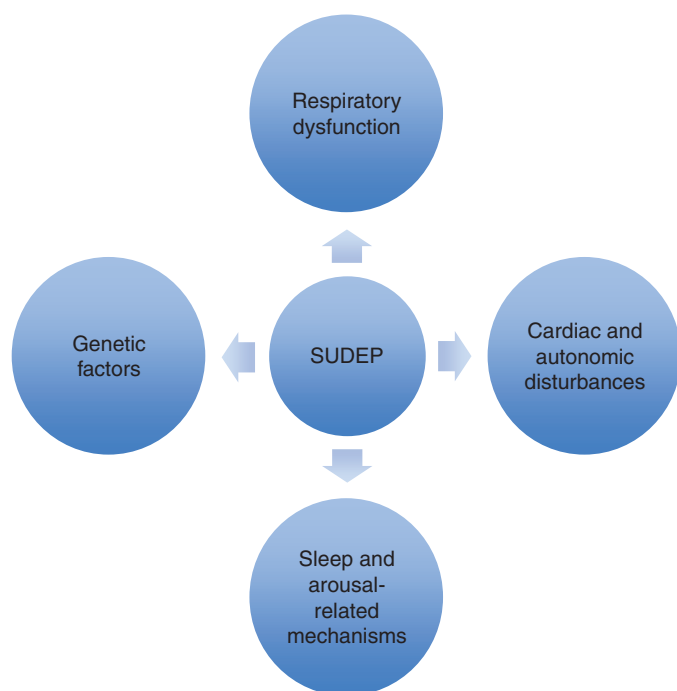


FIGURE 43.1 Possible mechanisms of SUDEP.

TABLE 43.3 Cardiac Mechanisms Contributing to SUDEP

Predisposing Cardiac Abnormalities
Neurocardiac channelopathies
Decreased heart rate variability
Chronic autonomic changes
Antiepileptic medications
Periictal effects of seizures
Neurotransmitter release
Ictal arrhythmias
Ictal cardiac ischemia

Source: Adapted from Ref. (8). Bermeo-Ovalle AC, Kennedy JD, Schuele SU. Cardiac and autonomic mechanisms contributing to SUDEP. *J Clin Neurophysiol.* 2015;32:21–29.

as well as cardiac and autonomic dysfunctions resulting at times in fatal arrhythmias. Mouse models of Dravet syndrome that is often caused by voltage-gated sodium channel *SCN1A* gene mutation have demonstrated atropine-sensitive ictal bradycardia and premature death. Brugada syndrome (due to a mutation in *SCN5A* gene) has been described to coexist with cases of cryptogenic frontal lobe epilepsy and cause electrocardiographic (ECG) abnormalities that could be made worse by fever, alcohol, or sodium channel blockers. In patients with no structural heart disease and no known ECG abnormalities, polymorphic ventricular tachycardia has been seen due to the surge of catecholamine release in response to exertion or emotional stress. In some of these cases, mutations in the ryanodine receptor gene *RYR2* and calsequestrin 2 (*CASQ2*) genes have been reported.

Cortical stimulation in humans and animals has also shown that the limbic regions usually affected by seizures including the cingulate gyrus, insula, orbital frontal regions, and amygdala play a role in the central autonomic regulation of the heart. Acute transient changes in heart function are seen acutely in seizures especially generalized convulsive seizures, but chronic changes in cardiac tone have been reported in the form of decreased heart rate variability. During the acute ictal phase, 39% of patients with refractory epilepsy have been reported to have one or more periictal arrhythmias or repolarization abnormalities. Patients with SUDEP were also found to have a higher maximum ictal heart rate and greater increase in heart rate associated with seizures arising from sleep compared to patients with refractory epilepsy who had not succumbed to SUDEP. While ictal tachycardia is seen in 76% to 99% of patients in epilepsy monitoring units (EMU), ictal bradycardia is seen only in 2% to 4% of cases and more often seen with temporal lobe-onset seizures. Ictal asystole is rare and reported in 2.7–4 per 1,000 patients in the EMU, often reported with an impaired vagal response that confers a higher risk of cardiac death. Interestingly, asystole does not occur with every seizure in an individual patient, raising the question as to what specific ictal factors predispose to ictal asystole in a predisposed individual.

Sleep and Arousal Mechanisms

The predilection for SUDEP to occur at night and during sleep has raised the suspicion for the roles of sleep and arousal systems in SUDEP. The role of impaired consciousness in epilepsy has contributed to the understanding of these mechanisms in SUDEP (9). The “network inhibition hypothesis” that attempts to explain the impaired consciousness seen in the setting of focal temporal seizures hypothesizes that removal of the subcortical arousal leads to sleep-like activity in the bilateral frontoparietal association cortices and hence impaired consciousness. Animal models have been devised to test this hypothesis, with findings that low serotonin levels may induce impaired ventilation and arousal responses to carbon dioxide. The role of the serotonin system in the pathophysiology of SUDEP and sudden infant death syndrome (SIDS) has emerged as a potential target for treatment with selective serotonin-reuptake inhibitors. In animal models, serotonergic neurons have been shown to be vital to detect increases in blood carbon dioxide levels and to increase breathing and arousal from sleep.

In addition, increased adenosine levels induced by a seizure coupled with decreased metabolic clearance of adenosine were found to cause seizure-related respiratory arrest and possible fatal apneas leading to the “adenosine hypothesis of SUDEP.” Experimental use of caffeine in animal models showed some protection against SUDEP in this setting.

The role of postictal generalized EEG suppression, defined as postictal unilateral or bilateral EEG suppression lasting more than 1 second and occurring within 30 seconds of seizure cessation with an amplitude of less than 10 microvolts, has been the subject of significant debate (10). This suppression may reflect enhanced activity of inhibitory neuronal networks and may be augmented by sleep and hypoxia.

Genetic Factors

With the recent trend toward organized genetic research in epilepsy, candidate SUDEP genes associated with control of respiration and arousal, and expressed in respiratory, cardiac, and autonomic pathways are being evaluated. The most clear clinical example of the importance of genetic factors in SUDEP is present in children with Dravet syndrome where the *SCN1A* mutation confers a complex interaction between abnormal channel variants and risk for cardiac arrhythmias and respiratory disturbances. Animal models that investigate the role of sodium and potassium channel mutations as well as other possible genetic factors are being designed. A list of genes that may potentially increase the risk for SUDEP may be found in Table 43.4 (11).

RISK FACTORS FOR SUDEP

All of the work to establish the mechanisms underlying SUDEP aim at identifying the risk factors that would help recognize patients with increased risk for SUDEP and



**TABLE 43.4 Selected Gene Mutations That Potentially Increase the Risk of SUDEP**

GENE	PROTEIN	ASSOCIATED HUMAN DISEASE
SCN1A	Voltage-gated sodium channel Nav1.1	Dravet syndrome
SCN5A	Voltage-gated sodium channel Nav1.5 (loss of function mutation)	Brugada syndrome
SCN5A	Voltage-gated sodium channel Nav1.5 (gain of function mutation)	Long QT syndrome type 3
KCNA1	Voltage-gated potassium channel Kv1.1	Not applicable
KCNH2	Voltage-gated potassium channel Kv11.1	Long QT syndrome type 2
KCNQ1	Voltage-gated potassium channel Kv7.1	Long QT syndrome type 1
HTP2C	5-HT <sub>2C</sub>	Not applicable
RYR2	Ryanodine receptor 2	Catecholaminergic polymorphic ventricular tachycardia

Source: Adapted from Ref. (11). Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. *Nat Rev Neurol*. 2014;10:271–282.

ultimately institute the right preventive measures. A combined analysis of the risk factors for SUDEP from published case-control studies of SUDEP with live controls yielded the following findings (12). It was found that increased frequency of generalized tonic-clonic seizures, use of polytherapy, duration of epilepsy, young age at onset, male gender with age of onset less than 16 years, symptomatic etiology, and lamotrigine therapy were significantly associated with SUDEP. Reanalysis and evaluation of multiple randomized controlled trials involving lamotrigine and other antiepileptic drugs (AEDs) have failed to establish any significant association between any particular AED use and SUDEP. Prone position, substance use, cognitive impairment (Full scale IQ < 70), and alcohol use have also been found in other studies to possibly contribute to SUDEP. Other factors discussed in the section on the mechanisms of SUDEP may also play a role in the increased risk for SUDEP.

### PREVENTION OF SUDEP

As more of the risk factors for SUDEP are revealed, it has become possible to identify patients with increased risks and to develop strategies to decrease these risks (13). The best described risk factor for SUDEP at this time is the occurrence of frequent generalized tonic-clonic seizures. Hence, any therapy

that reduces the frequency of these seizures decreases SUDEP risk, be it specific AEDs or epilepsy surgery. Moreover, SUDEP risk may be decreased by reducing other risk factors including the longer duration of epilepsy, poor adherence to treatment, and addressing the comorbidities in epilepsy.

The use of beta blockers, pacemakers in cases of ictal asystole, caffeine, and selective serotonin reuptake inhibitors has been contemplated with no proven reduction of SUDEP at this point.

At times, parents and caregivers may be interested in seizure detection devices that would permit them to detect seizures earlier and institute early interventions. These devices use a combination of one or more methods to detect seizures. Noninvasive sensors like accelerometers may be used in devices worn by person with epilepsy to detect seizure-related motion. To detect nocturnal seizures, mattress motion or video motion detection devices may be used. Some devices use physiological parameters such as pulse oximetry, heart rate, or electrodermal activity to detect changes seen with seizures. Unfortunately, most of these devices have high false-positive alarm rates that may negatively affect the quality of life of patients and caregivers. It is important to note that none of these seizure detection devices have been proved to prevent seizures or SUDEP. Similarly, the role of nocturnal supervision and intervention in preventing SUDEP remains to be proven. Multiple studies have shown that nursing interventions, including oxygen supplementation, oropharyngeal suctioning, and patient repositioning, can reduce respiratory dysfunction in the postictal period. The role of patients as well as their caregivers is also important in reducing the risk of SUDEP. Behavioral modifications including attention to triggers like sleep deprivation, alcohol use, and AED nonadherence could decrease mortality in patients with epilepsy and improve their seizure control. It is important in this regard to inform patients with epilepsy about SUDEP so that they can actively participate in the strategies that reduce their risk and prevent SUDEP.

### SUDEP COUNSELING

The discussion of SUDEP could be a daunting task for patients and physicians alike. With the paucity of other guidelines, the NIH/NINDS workshop on SUDEP recommended the following in discussing the important topic of “the right to know versus the right not to know” (14). Except for patients with cultural or psychological circumstances that preclude safe discussion, the benefit of discussing SUDEP outweighs the harms that could occur. This is especially true in patients with generalized tonic-clonic seizures. This counseling could be done as part of the education about living with epilepsy.

In the authors’ experience, it may be best to introduce the concept that seizures can be very rarely fatal in the initial discussion about epilepsy and risks of death in the settings of injuries, drowning, and status epilepticus. If patients ask specific or direct questions, it is recommended to answer frankly and to have epilepsy education materials available that discuss SUDEP. In cases of refractory seizures, a more

**TABLE 43.5 SUDEP-Related Organizations and Resources****SUDEP-Specific Organizations and Resources**

Centers for Disease Control (SUDEP site)  
 Chelsea Hutchison Foundation  
 Citizens United for Research in Epilepsy (CURE)  
 Danny Did Foundation  
 North American SUDEP Registry (NASR)  
 Partners Against Mortality in Epilepsy

**Bereaved Parent or Grandparent Resources**

Compassionate Friends  
 Mothers In Support and Sympathy (MISS Foundation)  
 AGAST: Alliance of Grandparents: A Support In Tragedy  
 Sudden Unexplained Death In Children Program (SUDC)  
 Griefnet.org

**General Counseling and Support Regarding Loss Resources**

Association of Death Educators and Counselors (ADEC)  
 Local grief and loss centers in your community

**Medical and Investigative Resources**

Centers for Disease Control and Prevention: SIDS and SUID  
 National Association of Medical Examiners (NAME)  
 International Association of Coroners and Medical Examiners  
 National MCH Center for Child Death Review

Source: Adapted from Ref. (13). Partners against mortality in epilepsy conference summary. *Epilepsy Curr.* 2014; 14(Suppl 6):14–31.

detailed discussion about SUDEP may be warranted, especially when considering major treatment options including AED initiation, AED withdrawal, and epilepsy surgery.

In families of patients who succumb to SUDEP, it is important to respect the grieving of the family members and caregivers and to have available a list of SUDEP-specific organizations and resources (Table 43.5).

The best way to reduce SUDEP risk is to reduce seizure frequency. A wealth of research on the epidemiology, risk factors, and mechanisms of SUDEP is underway and

hopefully will improve the current understanding and management of SUDEP. Meanwhile, it is important to talk about SUDEP to patients with epilepsy so that they can join the fight to reduce the risk for SUDEP and potentially save their lives by actively participating in establishing and maintaining adequate seizure control.

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# EMU Safety Concerns

*Susan Hollar and Deborah LaBelle-Scarfo*

There are a variety of challenges, details, and protocols associated with epilepsy monitoring unit (EMU) admissions. While any inpatient admission involves many challenges, this patient population comes with a unique set of safety concerns. Many issues have not been researched enough to provide a uniform standard of care among all epilepsy centers. Recent focus on patient safety in the EMU has encouraged discussion and facilitated a move toward standards of safe care in the EMU. In 2010, the National Association of Epilepsy Centers (NAEC) published guidelines for epilepsy centers that emphasized the need for safety protocols (1). On March, 30, 2012, the Institute of Medicine (IOM) released a landmark report on the epilepsies titled, “*Epilepsy across the Spectrum: Promoting Health and Understanding*” (2). The report highlights numerous gaps in the knowledge and management of epilepsy and recommends actions for improving the lives of those living with this disorder. Successful monitoring in the EMU requires a balance between the risks associated with seizures and the need to gain diagnostic data (3).

## MEDICATION TAPERING

Management of the patient’s antiepileptic drugs (AEDs) for the monitoring admission should be considered carefully. AED withdrawal is the most common technique used for seizure provocation (1). The concern of AED taper or withdrawal causing status epilepticus is primary. It is of vital importance for the treating physician to be familiar with the patient’s history regarding prior AED changes or tapers, the patient’s response to such changes, and current seizure frequency. Clear, concise directions should be given to the patient regarding how AEDs will be tapered or withdrawn during their EMU admission. Careful consideration is given to the tapering or withdrawal of AEDs before admission for safety reasons. Updates regarding changes to the patient’s AED regimen should be given to the EMU patient and their family members daily. Often the goal of this admission is to capture a number of the patient’s typical seizures; however, any change in AED regimen creates the risk of altering the

seizure type. The patient who has complex partial seizures on a regular basis may have only tonic-clonic seizures due to medication changes.

Considerations involving the tapering/withdrawal decision can be straightforward, while other factors affecting the patient merit consideration. Depending on the facility’s admission process, elective admissions may be up for cancelation if the hospital’s overall census is at a maximum level. Availability of the specific room needed for monitoring, waiting for patient discharges, and getting rooms cleaned all have the potential of placing the patient scheduled for admission to the EMU without a room, or waiting in the admissions area for a prolonged period of time. These situations have to be considered when holding or tapering AEDs prior to the actual admission. A patient that has a seizure in the admissions area is a patient sent to the emergency department (ED) regardless of the severity of the seizure. This situation creates added frustration for the patient, causes potential delay of monitoring, and additional expense for the patient and or their insurance company.

The other consideration when making the determination of tapering or withdrawing medications is length of stay. Delaying a taper until admission may result in an extended length of stay. In the authors’ experience, this fact has become a greater influence on protocol than it would have several years ago. These factors can elevate the risk of safety issues before the patient enters the EMU.

Patients trust that the monitoring unit is well equipped to keep them safe in the event of a seizure. It is imperative that rescue protocols are clearly written and that the staff and covering physicians are well versed in these protocols. From a safety standpoint, it is imperative that protocols be current, written clearly and concisely, and be readily available for staff to follow. Seizure rescue protocols should include when to initiate rescue medications, defined type of seizure, length of time that a seizure lasts, number of seizures in a specific time period, what type and dose of rescue medication to administer, and any repeat orders for same. Protocols should also define criteria for the staff’s

observation of the patient's postictal period to ensure safe recovery from a seizure.

### PATIENT OBSERVATION

All safety measures revolve around the patient's behavior during an event. One of the most challenging pieces of care in the EMU is how to provide continual observation of the patient. Before the NAEC's 2010 guidelines, there were no mandates for continuous monitoring of patients in an EMU. The 2010 guidelines for continuous observation of patients in the EMU provide current best practice (4).

Current technology provides expanded options for continuous real-time observation. There are as many variations of accomplishing this as there are EMUs. The critical service the observer provides is their attentiveness to the patient's seizure behaviors. It is preferred that they have the ability to recognize ictal activity and to alert staff in a timely manner to provide seizure assessment and emergency rescue, if needed. Some EMUs rely on the patient's family to provide in-room observation. Relying on a family member for a 24-hour observation has obvious limitations. At times, this observation may be supplemented with in-room sitters. Many centers utilize staff to observe patients by live remote observation. A staff member trained in behavior observation, camera control, and a mechanism to alert nursing staff (remote observer) is the accepted minimum of care. A combination of all of the above is ideal.

### FALLS AND INJURIES

Falls risk in any hospitalized patient is of great concern. The patient with epilepsy should be considered to have an elevated risk for falls while an inpatient in the EMU, particularly if they have a history of falls with seizures (5). If a patient requires hospitalization for continuous monitoring in an EMU, they should be considered a fall risk regardless of their final diagnosis or medications. Careful screening by the healthcare team upon admission is of vital importance. There are several approaches to this safety risk. Some units implement a tiered approach based on the patient population. Patients who are not having any of their AEDs adjusted, with no known history of generalized seizures and no history of falls are considered low falls risk and receive no additional safety measures. Patients who do have adjustments made to their AED regimen, or have known generalized tonic-clonic seizures are considered high risk for falls. This population should also have an activity level ordered by the provider of "out of bed with assist only" restrictions. Patients can be given a safety belt device to be worn while out of bed. Some organizations allow the patient to opt-out of the use of the belt. This requires a document that clearly explains the risk of injury from falling during the admission. The patient must agree to release the facility from responsibility of injury sustained as a result of a fall. Then again, many centers do not offer an opt-out option for this population. Each facility

has its own set of highly visible identifiers to use for the high falls risk population. Special colored nonskid socks, bracelets, door markers, and chart markers are commonly used to identify the patient at risk for falls.

Many EMUs require patients undergoing phase II monitoring with intracranial electrodes to utilize the belt, to use a bedside commode, and require "up to chair with full assist" restrictions. The few studies that have been conducted demonstrate most falls or injuries occur when the patient is in the bathroom. This supports the use of bedside commodes for the highest-risk patients, which includes all surgical patients. When patients refuse to use a bedside commode, the care nurse should be present outside of the bathroom door with the door ajar so that they can respond quickly to a seizure that may occur while the patient is toileting. Other less restrictive measures include requiring an adult family or friend observer who remains with the patient at all times. The observer alerts the staff to any seizure or event putting the patient at risk. Patients should be placed on falls precautions and be out of bed with assist only.

The balance of quality of life and minimizing risk of fall or injury while being monitored is a difficult balance. Acknowledging the restrictions and explaining the reasons for the additional safety measures is the best approach for all parties involved.

The room environment is an additional safety concern. The bed should be equipped with padding on the side rails to avoid injury to the patient. Bed pads that are custom made for the bed fit best around the rails. If these are not available, heavy blankets securely taped around the railings can be utilized. Some organizations utilize floor pads beside the bed, but there are no supporting studies on the benefit of the padding.

Intravenous (IV) access for drug administration is established upon admission. When IV access is not possible, an alternative method for drug administration should also be established at the beginning of the monitoring admission (6).

Daily activities such as bathing, dressing, and eating are already modified during the monitoring admission. During bathing and dressing, a family member or staff member should be present in the room in the event of a seizure while the patient is off camera. Patients should bath at bedside or with their observer present in the bathroom. Surgical patients should bathe at bedside with assistance from nursing staff.

Exercise while being monitored in an EMU is often achieved with a stationary bike for the patient with scalp electrodes only. This should only be allowed with staff assistance in the room. Surgical patients should not be allowed on stationary bikes. A safer option for this patient is a hand-operated pedaler that allows the patient to remain seated in the bed. Surgical patients may require compression stockings and compressive devices to reduce the risk of deep venous thrombosis.

The minimum requirement guidelines from the NAEC (1) are to provide a staff member to be in constant observation of the patient being monitored. This requirement reduces the incidence of falls as well as the response



time for staff to arrive in the room in the event of a fall or seizure. Remote observers trained to identify behaviors for each patient can significantly reduce injuries to the patients (6). If the remote observers are in close proximity and are trained in seizure rescue, the response time is greatly reduced. The effectiveness of those responsible for observing the patient on the monitor must be assured. The alertness and concentration of the observer must be taken into consideration. Studies indicate periods of time greater than 8-hour shifts decrease the ability to concentrate. The number of patients a remote observer can effectively monitor at one time has not been determined. Providing two remote observers for each shift allows for one to respond, take a break, and assure alertness of the other observer.

Remote observers must be provided with a description of the typical event for each patient being observed. This should include specific details for the onset of each type of seizure. This allows the observer to focus on early detection of the event onset without depending on the patient or family member. If the observer is not in a situation to respond to the event, a quick method to alert nursing staff must be established (ie, an emergency phone or alarm).

## EDUCATION OF STAFF AND PATIENT'S FAMILY

Nursing care in the EMU focuses on the needs of the patient and should be based on current best practice. Competencies in the care of patients with seizures should be developed to include knowledge of seizure types; the goals of EMU monitoring, ictal and postictal care, and seizure safety (7). Care nurses should demonstrate competency that seizure precautions for each patient are instituted upon admission to the EMU. This includes Falls Risk Assessment, functioning suction equipment, the ready availability of supplemental oxygen supplies, proper room set up per established seizure precaution protocols, and adequate response to a seizure. The care nurse should also know the importance of getting the patient's seizure history from the patient and the patient's family member to help plan for their care. The nurse's role is to observe, keep the patient safe, and record the details of a seizure. EMU nursing staff should be trained in the importance of testing a patient during a seizure, making sure that nobody is blocking the camera and that the patient is uncovered so that the patient's motor response during and after a seizure can be recorded. Research indicates that specialty training, in-services, lectures, and continuing education classes all increase the nurse's confidence in caring for this population (7). Education should be provided by personnel who specialize in the care of the patient with seizures. Many epilepsy centers employ a nurse or an advanced practice provider who specializes in the care of this population. Periodic lectures given by the epileptologists also enhance the staff's knowledge and confidence level as well as team building between caregivers. Creating a resource guide is also helpful, whether it is available as a paper book or electronically. It is best practice to have

this information in one spot, known to all care nurses in the EMU.

Educating the patient's family member(s) is also important. The family member should be instructed on location of seizure notification devices as well as nurse notification devices to help in the response time and data gathering. The family member can be integral in testing the patient's awareness during a seizure. The family member may also serve as the best witness of the patient's seizure characteristics.

## DISCHARGE PLANNING

Discharge planning for the EMU patient who has had AEDs tapered or withdrawn is as important as the admission plan. The EMU patient's discharge plan begins upon admission. Once the data needed to make a diagnosis are obtained, AEDs are restarted. The provider and the patient work together in the decision to maintain the current medication regimen or to change it in some manner. A patient typically remains an inpatient for 24 hours once medication is restarted. There should be adequate time for the levels to be therapeutic before discharge. This may require additional doses. If they have rescue medication prescribed, they should have access to that for the travel home. It should be recognized that most EMUs do not allow inpatients to have their home medications with them, so they may not have their home rescue medications upon departure from the hospital.

## PHASE II ELECTRODE SET UP

It is important to have qualified technologists involved in the Phase II monitoring set up. Protocols to verify input naming, location, and montage set up should be developed and utilized. This should include verification with neuroimaging post grid or strip placement. This program requires two qualified technologists to be involved in the hook up (8). During the hook up, the two technologists should be in protected time, where they are not allowed to be interrupted in an effort to minimize errors. The set up begins with a map of the intracranial electrode placement drawn by the epileptologist or the surgeon. Documentation of the inputs and maps should be maintained as part of the monitoring record. Once the inputs have been entered and the cables connected, verification of the set up should be documented.

The physical hook up is an important phase as well. The cables should be secured with a stress loop on the top of the patient's head. All cables should be routed and secured as much out of the patient's reach as possible. A technologist should be present when dressing changes occur to ensure the safety of the cables and that all cables remain intact.

It is recommended that patients with intracranial grids or strips undergoing MRI scanning have the cables separated so they are not touching each other or overlapping. Some manufacturers offer boots to cover the ends of the electrodes for MRI scanning purposes; they should then be separated and secured for the scan.

Patients admitted for monitoring to the EMU require balancing their experience with many safety measures. These patients are particularly vulnerable to injury, as often their AEDs have been tapered in an effort to provoke seizures. Each patient admitted to the EMU deserves individual consideration of their specific needs by all members of the care team.

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